THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

VOL. 58 JULY, 1947 NO. 1

RECENT DEVELOPMENTS IN MEDICAL PHYSICS HAVING APPLICATION TO RADIATION THERAPY*

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IN SURVEYING recent developments in medical physics that possibly have application in radiation therapy, I have nothing spectacular to review, nothing of any immediate issue in radiation therapy.

I would like merely to spin a tale of work which is currently being done in some of the laboratories in the country, some in our own laboratory, all of which will have application to the general field of radiation therapy.

Much of the work in radiation therapy hinges around the use of radiation of radioactive isotopes. They are useful in two ways: (1) by specific localization of radioactive material, and (2) as tools for the study of metabolism. There are already certain radioactive compounds which can be made to accumulate only in certain normal tissues, and their radiation is expended where the radioactive substance is located. So far specific localization has been possible only for normal tissues but it is possible that, similarly, neoplastic tissue might specifically absorb certain compounds.

As yet there have been discovered no substances with true specific localization in neoplastic tissue. Radioactive phosphorus has been generally used to give local and general radiation therapy. When radioactive phosphate is administered the phosphate is slightly concentrated in neoplastic tissue but it is generally distributed in the whole body, and the most we could hope for as a concentration of the radioactive phosphate would be approximately twice as much in the neoplastic as in the normal tissues.

Besides phosphorus, strontium has been used, but here again no specific localization has been found in neoplastic tissues. An excellent example of a specifically localizing radioactive isotope is radioactive iodine. The normal thyroid gland certainly concentrates radioactive iodine if it is administered in small amounts. This method has been used successfully to irradiate the thyroid, and this form of specific irradiation depresses the activity of the hyperactive thyroid gland; but, as far as approaching the ultimate goal in the use of isotopes —that we might be able to find a substance that would localize in neoplastic tissue to a

* Presented at the Twenty-eighth Annual Meeting, American Radium Society, San Francisco, Calif., June 28–29, 1946.

great extent—that goal has not been achieved.

However, the results of recent investigation are promising. In certain instances we are able to localize in other tissues specific amounts of these artificial radioactive isotopes. Chromic phosphate when administered intravenously will go to the normal liver and spleen in about equal concentrations. This is an ideal situation for studying the specific effect of radiation upon these two tissues. Again we have little use of chromic phosphate for applying radiation therapy to these organs invaded by neoplastic disease. In neoplastic diseases of the liver, the chromic phosphate concentrates only in the normal liver tissue. Irradiation of neoplastic tissue is at the expense of irradiation of the normal tissue.

We anticipate the development of compounds which will localize in a given neoplasm. Chromic phosphate can be used experimentally to give local radiation of tissues if it is not introduced by infusion of the tissues. We hope to develop work along this line to find out factors which will help to make for uniform spreading of this inert radioactive compound through the tissues so that localized areas can be specifically irradiated. So far we have been unable to develop a compound which will do anything but stay at the exact site where the needle introduced it into the tissues. It is not impossible to look forward into the future when we will be able to say we have a compound which will spread uniformly through the tissues. This would be useful for selective irradiation of skin, subcutaneous tissue, and lymphatic tissue.

A method that is promising is to find some compound which through a phase of physiological chemistry might become built into the neoplastic tissue preferentially. Such a substance might be synthesized with radiocarbon, radiohydrogen, radiohalogens, or radiophosphorus. It is not hopeless to think perhaps that some precursor of nucleic acid or even some simple substance such as an amino acid might be taken up with great selectivity by neoplastic tissue and not by the rest of the body. A disease such as melanosarcoma should be amenable to this research. With the existing knowledge of melanin chemistry it should be possible to build radioactive carbon into precursors of melanin which is formed in great quantities by the neoplasm. The melanosarcoma would thus be given specific localized radiation from the contained radioactive carbon.

A great deal of work by Hevesy on nucleic acid metabolism appeared during the war which is of extreme interest. He has shown that in the case of two neoplasms growing in the same animal if one of the tumors is irradiated with roentgen rays and the rest of the animal not irradiated, that simultaneously after the irradiation, there is a decrease in the nucleic acid turnover in the irradiated tumor and the non-irradiated tumor. The non-irradiated tumor received no direct irradiation, but depression of nucleic acid synthesis is striking and could only have been mediated by a chemical substance moving from the irradiated tumor into the blood. This substance depresses nucleic acid metabolism either of the animal as a whole or of the other tumor specifically. Such an indirect effect of irradiation gives us hope that perhaps the neoplastic growth inhibiting mechanism associated with tissue irradiation is a chemical substance and is not due to tissue ionization directly. It should be possible to localize and identify such a compound, and it is reasonably likely that it can be used therapeutically when found. Perhaps future radiation treatment will be by the use of such a chemical compound and not by the direct irradiation of the tissue.

There is some work now in the experimental stage to develop new forms of applying radiation therapy. The betatron, as is well known, for the past several years has been able to develop 20 million volt gamma rays and beta rays which are available for radiation therapy. The advantage of such high energy particle gamma rays is that the maximum ionization is not at the body surface at the point of entry of the radia-

tion beam. On the contrary, the ionization increases progressively beyond the surface. In the case of beta radiation from the betatron of 20 million volts energy, one can irradiate tissues as deep as 12 centimeters to an extent of twice the skin dosage. This tissue depth dose is quite different from the conventional type of roentgen therapy or million volt roentgen therapy.

Now if we are interested in the betatron, we probably would also be interested in the other advances that are currently going on in the general field of physics. There are not only betatrons producing high energy particles, but there are particle accelerating machines (cyclotrons, cyclo sychotrons, linear accelerators, etc.) which will produce very high energy beta, alpha, proton, and deuteron particles. There is an indication of a future tendency in radiation therapy that accelerated protons of the 100 million volt magnitude are even more promising for certain types of tissue irradiation than accelerated electrons.

Dr. Wilson of Harvard University expects to be able to demonstrate that the dosage ratio of the surface of the skin compared to the deeper tissues might be as high as one hundred to one in favor of the radiation of deeper tissues. This, of course, would not necessarily revolutionize common roentgen therapy, but it would make available to the roentgenologist a new tool which would give an especially well localized irradiation of deeper tissues when such is a desired therapy.

We have reason to hope in the future for the finding of substances which, either by metabolic sequences or by physical properties, can be localized in certain neoplasms so that neoplastic diseases may be treated by self-contained radiation. However, these goals have not been realized. We do feel that if we really understood the biology of neoplastic disease methods other than tissue irradiation might be developed which would be more effective. We believe the best hope for cancer control is with the use of radioactive isotopes because their powerful use as tracers and dynometers of metabolic processes will result in a working understanding of normal and neoplastic metabolic processes. Only when we have accumulated more knowledge of metabolism can effective ways be found to eradicate neoplastic disease by methods other than by radiation therapy and surgery.*

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* For discussion see page 30.

RADIOACTIVE PHOSPHORUS AS AN EXTERNAL THERAPEUTIC AGENT IN BASAL CELL CARCINOMA, WARTS AND HEMANGIOMA*

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SINCE the discovery of natural radioactivity and the recognition of cathode rays as high speed beta particles, attempts have repeatedly been made to utilize beta radiation in the treatment of skin diseases. It has long been appreciated that beta radiation is particularly suitable for the treatment of superficial lesions of the skin, because beta rays penetrate the skin to a depth of only a few millimeters, thus reaching all layers of the skin without penetrating to deeper structures. It is also known that the general biological effect of beta rays is similar to that of other ionizing radiations such as roentgen rays or gamma rays; that is, when beta rays are applied in sufficient quantity they are capable of destroying living cells. Until the discovery of artificial radoactivity, available sources of beta radiation were either naturally occurring radioactive substances or specially constructed cathode-ray tubes. Neither of these sources, however, provides pure beta radiation. The lag in the development and establishment of beta radiation therapy has been due in large part to this fact, although the complex problem of dosage, and the primary interest in the therapeutic use of gamma rays have contributed to delaying progress in this field. The discovery of artificial radioactivity has made available substances which radiate beta particles only. Radioactive phosphorus (P^{32}) is one such substance. P^{32} disintegrates at a daily rate of 4.8 per cent and thus loses one-half of its initial activity in 14.3 days. The maximum penetration of P^{32} beta particles in water or tissue is approximately 8 mm. One must realize, however, that the energy of the P^{32} beta particles varies from 0 electron volts to 1.69×10^6 e.v.; therefore only a relatively small percentage actually penetrates to the 8 mm. depth. Absorption measurements have shown that approximately 48 per cent of the radiation from P^{32} is absorbed in the first millimeter of water or tissue and that the absorption is practically exponential. The radioactive phosphorus which has been used in these studies is an aqueous solution of disodium hydrogen phosphate containing 15 mg. of the salt per cubic centimeter of water.

The present studies were started in 1941 and after an interruption of one year were resumed in 1943. Despite the obvious possibilities of using P^{32} solution for external application to the skin, difficulties were encountered in developing a technique which would insure exactly reproducible exposures and reactions. After experimentation with absorbent cotton, vaseline, lanolin, blotting paper, gum acacia, higher alcohols and other substances, it was found that ordinary thin blotting paper is a most suitable vehicle. Blotting paper of known dimensions soaked in measured amounts of radioactive Na_2HPO_4 solution, and dried, can be

TABLE I

Degree of Reaction	Microcuries per sq. cm.
Threshold erythema	34
Mild erythema	approx. 620
Marked erythema	approx. 1250
Severe erythema	approx. 1850
Mild epidermitis (dry, scaly)	approx. 2500
Marked epidermitis (scaly or bullous)	approx. 3200
Severe epidermitis (epidermolysis)	approx. 4400

* Presented at the Twenty-eighth Annual Meeting, American Radium Society, San Francisco, Calif., June 28–29, 1946.

FIG. 1. G.B. Basal cell epithelioma, right side of the face. (*a*) Before treatment. (*b*) One year after four treatments. One of the earliest cases treated (in March, 1943). Total dose of radioactive phosphorus approximately 9,000 microcurie-hours. No recurrence and no further skin changes for three years.

FIG. 2. J.D.B. Basal cell epithelioma, left side of the face and forehead (intradermal). (*a*) Before treatment. (*b*) Seven months after two treatments. Dose of radioactive phosphorus 6,600 microcurie-hours per square centimeter.

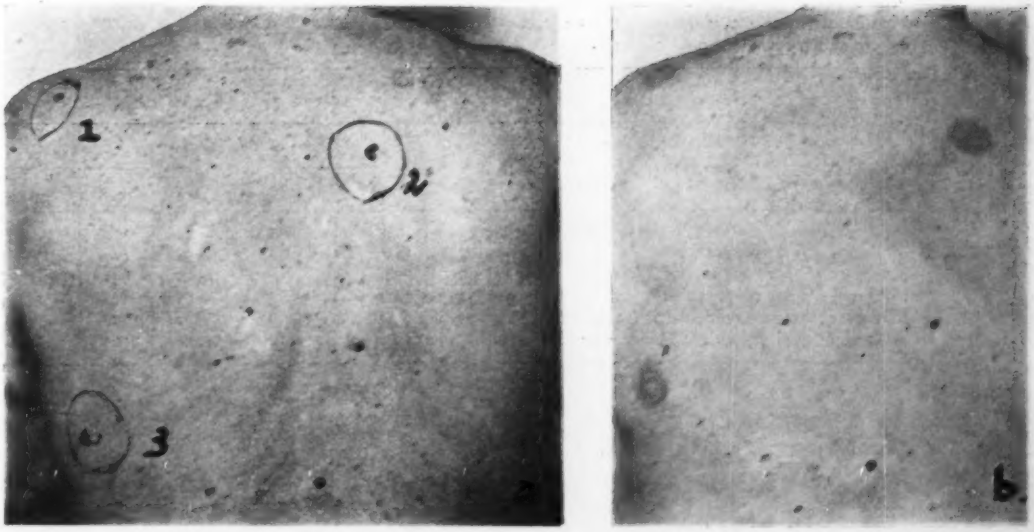


FIG. 3. H.H.B. Multiple basal cell carcinoma and hyperkeratoses. (*a*) Before treatment. (*b*) Forty-five days after treatment. Lesions 1 and 2, 2,000 microcurie-hours per square centimeter; lesion 3, 2,600 microcurie-hours per square centimeter. Treated April, 1944. No recurrence.

applied easily to any part of the skin. The following method of application has been developed: Office type blotting paper 0.4 mm. thick and weighing 21 mg. per square centimeter is cut to size to cover the lesion and to allow a safety margin from 0.3 to 1.0 cm., depending upon the type of lesion. The blotting paper is backed by some kind of adhesive tape, and placed on a good drying surface such as a radiator or electric plate at low heat. A measured amount of P^{32} solution is then soaked into the blotting paper which is left to dry. When completely prepared, the blotting paper is applied over

TABLE II-A

INITIAL MICROCURIES REQUIRED FOR VARYING DEGREES OF ERYTHEMA

Exposure Time: 24 Hours

Reaction	Area in Square Centimeters									
	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Mild erythema	12.3	24.5	36.8	49	61.3	73.5	85.8	98	110	123
Moderately intense erythema	24.5	49	73.5	98	123	147	172	196	221	245
Severe erythema	36.8	73.5	110	147	184	221	257	294	331	368
Mild epidermitis (dry, scaly)	49	98	147	196	245	294	343	392	441	490
Moderately intense epidermitis (scaly or wet)	61.3	123	184	245	306	368	429	490	551	613
Severe epidermitis (bullous epidermolysis)	85.8	172	257	343	429	515	600	686	772	858

Exposure Time: 48 Hours

Reaction	Area in Square Centimeters									
	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Mild erythema	6.5	12.9	19.4	25.8	32.3	38.7	45.2	51.6	58.1	64.5
Moderately intense erythema	12.9	25.8	38.7	51.6	64.5	77.4	90.3	103	116	129
Severe erythema	19.4	38.7	58.1	77.4	96.7	116	135	155	174	193
Mild epidermitis (dry, scaly)	25.8	51.6	77.4	103	129	155	181	206	232	258
Moderately intense epidermitis (scaly or wet)	32.3	64.5	96.7	129	161	194	226	2258	290	323
Severe epidermitis (bullous epidermolysis)	45.2	90.3	135	181	226	271	316	361	406	451

TABLE II-B

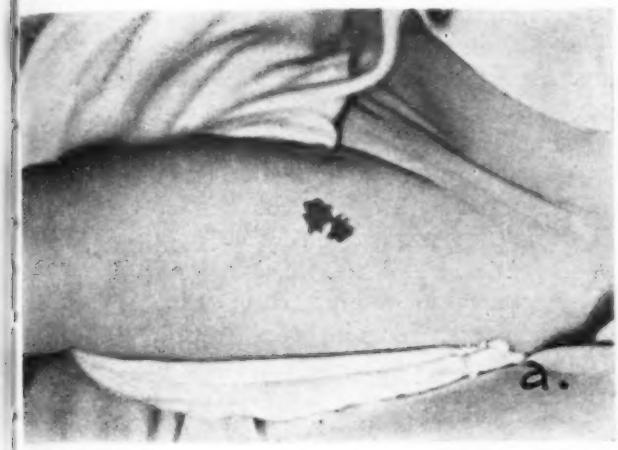
INITIAL MICROCURIES REQUIRED FOR VARYING DEGREES OF ERYTHEMA

Exposure Time: 72 Hours

Reaction	Area in Square Centimeters									
	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Mild erythema	4.6	9.1	13.7	18.2	22.8	27.3	31.8	36.4	41.0	45.5
Moderately intense erythema	9.1	18 2	27.3	36.4	45.5	54.6	63.7	72.8	81.9	91.0
Severe erythema	13.6	27.3	41.0	54.6	68.3	81.9	95.8	109.	123	137
Mild epidermitis (dry, scaly)	18.2	36.4	54.6	72.8	91.0	109	127	146	164	182
Moderately intense epidermitis (scaly or wet)	22.8	45.5	68.3	91.0	114	137	159	182	205	228
Severe epidermitis (bullous epidermolysis)	31.9	63.7	95.6	127	159	191	223	255	286	319

Exposure Time: 96 Hours

Reaction	Area in Square Centimeters									
	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Mild erythema	3.6	7.1	10.7	14.3	17.8	21.4	25	28.5	32.1	31.7
Moderately intense erythema	7.1	14.3	21.4	28.6	35.7	42.8	50	57.1	64.3	71.4
Severe erythema	10.7	21.4	32.1	42.8	53.6	64.3	75	85.7	96.4	107
Mild epidermitis (dry, scaly)	14.3	28.6	42.8	57.2	71.4	85.7	100	114	128	143
Moderately intense epidermitis (scaly or wet)	17.8	35.7	53.5	71.4	89.1	107	125	143	162	178
Severe epidermitis (bullous epidermolysis)	25	50	75	100	125	150	175	200	225	250



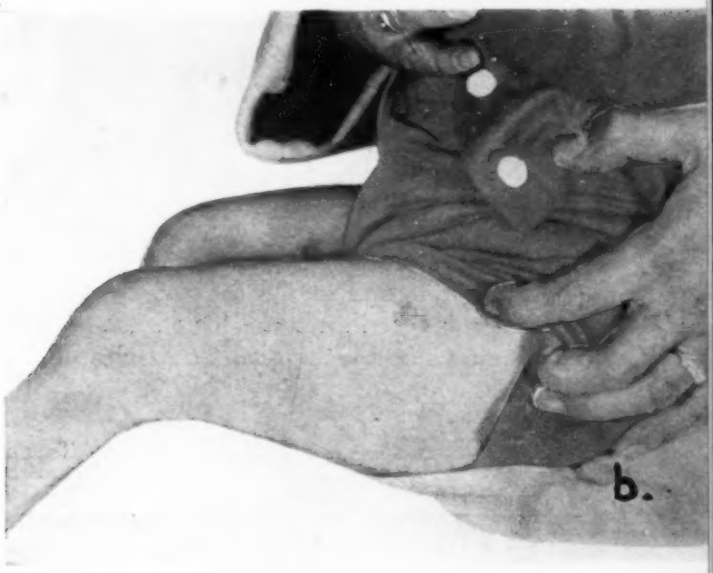


FIG. 4. H.C. Hemangioma, right thigh. (*a*) Before treatment. (*b*) Seven months after treatment. First and second treatments were ten weeks apart. Second and third treatments were six weeks apart. Each treatment approximately 200 microcurie-hours per square centimeter.

FIG. 5. S.J.St. Basal cell carcinoma on right side of neck (*a*) Before treatment. (*b*) Eleven days after beginning of treatment. Dose, 4,300 microcurie-hours per square centimeter. (*c*) Sixty days after beginning of treatment. No recurrence and no further skin changes for two and one-half years.

the skin lesion to be treated and secured in place if necessary with additional adhesive tape. It is left in place for a sufficient time to provide the desirable exposure for the condition under treatment. The exposure is calculated in microcurie-hours per square centimeter, since the reaction obtained will be a function of the area over which radiation is distributed and of the time of exposure. Once a technique had been established, the first question to consider was the evidently a function of the area over which the P^{32} is distributed, and of the time of exposure. Accordingly, it has been possible to compute the amounts of P^{32} required to produce certain reactions.

With the foregoing experimental data on hand therapeutic studies were undertaken. During the period from March, 1943, to October, 1945, 301 skin lesions were treated by external local application of P^{32}. Since October, 1945, some 100 additional

Table III

TREATMENT STATISTICS

Type of Lesion	Number of Lesions	Number of Treatments Required					Recurrence	No Conclusion. Patient Did not Return	Lesion Disappeared	Percentage of Lesions Disappeared
		1	2	3	4	5				
Basal cell carcinoma[1]	52	46	4	1*	1		1		51	98.0
Hyperkeratosis[2]	36	36							36	100
Verruca, hands[3]	132	104	13				6	9	117	88.6
Plantar wart[4]	50	44	3				2	1	47	94.0
Subungual wart[5]	16	12	3				1		15	93.6
Hemangioma[6]	17	3	2	4	4	2			2	

* Within two months.
[1] Three lesions were recurrences after curettement and desiccation; two lesions were recurrences after treatment with roentgen rays.
[2] One lesion was a recurrence after treatment with roentgen rays.
[3] Three lesions were recurrences after treatment with roentgen rays; one lesion a recurrence after treatment with acid.
[4] Two lesions were recurrences after surgery; two lesions were recurrences after treatment with roentgen rays.
[5] One lesion was a recurrence after treatment with roentgen rays.
[6] Two lesions disappeared (1944); fifteen lesions improved, still under observation.

development of erythema as a biological measure of the effect of P^{32} beta radiation on the skin. It was found that the minimum exposure which produces a faint but discernible "threshold" erythema is 34 microcurie-hours per square centimeter. Subsequent studies have shown that the intensity of the skin reaction increases with the exposure.

Erythema studies carried out on 12 subjects with a total of 61 exposures were studied.[1]

Prior to the clinical erythema studies it was experimentally proved that the distribution of P^{32} solution in blotting paper of the sizes used in the studies is uniform. As stated before, when the distribution is uniform the radiation dose delivered is

lesions have been treated but these are omitted from the present report because of the shortness of the observation period.

Table III shows the various types of lesions treated, and the outcome of treatment.

Figures 1 to 5 show some of the patients before and after treatment.

All patients with hyperkeratosis or carcinoma were seen by at least two members of the Visible Tumor Clinic of the University of California Hospital. In all cases of carcinoma there was unanimous opinion as to diagnosis. Biopsy was taken in most instances. When a patient had multiple lesions, biopsy was taken usually from only one lesion. The diagnosis of hyperkeratosis was based on clinical judgment alone, and it

Table IV

TREATMENT PLAN

Lesion	Dosage	Lesion	Dosage
Warty basal cell carcinoma with pearly margins	5000 microcurie-hours per sq. cm. at *least* 0.5 cm. safety margin	Verruca vulgaris*	2500–4000 microcurie-hours per sq. cm.
Flat, scaly basal cell carcinoma	3500–4500 microcurie-hours per sq. cm. at least 1 cm. safety margin	Verruca plantaris†	3000–4500 microcurie-hours per sq. cm. depending on depth
Flat hyperkeratosis	3500–4000 microcurie-hours per sq. cm. 0.5 cm. safety margin	Subungual verruca**	4000–5000 microcurie-hours per sq. cm.
Warty hyperkeratosis	3000–4000 microcurie-hours per sq. cm. 0.3–0.5 cm. safety margin; repeat if necessary in 8 weeks	Hemangioma‡	300–600 microcurie-hours per sq. cm.

* Scrape off horny surface before treatment with P^{32}.

† Wide range of dosage due to variation in depth of lesion. If one treatment without success within 6 weeks, then repeat treatment after scraping off surface thoroughly.

** Nail should be cut as short as possible before P^{32} pad is applied.

‡ Repeat in monthly intervals depending on response.

is possible that some of these lesions were early malignancies.

During the early stages of these studies, dosage of the radioactive phosphorus varied considerably among the cases treated. Observation of the reactions, and analysis of the different doses in relation to the therapeutic response has led to a pattern of dosage which is now being systematically employed (Table IV). This has completely supplanted the empiricism with regard to dosage of the earlier stages of this study.

One more word concerning dosage. One must be aware of the inadequacy of expressing the dose by giving the amount of the radiating source and the time of exposure. At present, however, this seems to be the least confusing and misleading dosage determination. The ultimate aim is to express the dose in some unit which will reveal more about the energy dissipated in the tissues. The applicability of the unit "roentgen" to energy dissipated from beta radiation is debatable. Should existing questions be resolved in favor of using the "roentgen," it should be qualified by employing the term "beta roentgen" in order to indicate that the energy dissipated is derived from a beta radiating source.

The purpose of this report is to demonstrate that artificially radioactivated phosphorus, as a pure beta radiator, can be used satisfactorily in the treatment of superficial skin diseases. It is true that there are other well established methods of treatment of skin diseases which have proved satisfactory, such as low kilovoltage roentgen rays, surface surgery, etc. Certainly there is no intention to advance the method described in this report in competition with such long established procedures.

Rather, the present study has served to emphasize the usefulness in a particular field of therapeutics of one of the many biproducts of the chain reacting piles established for the production of plutonium and uranium 235.*

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REFERENCE

1. Low-Beer, B. V. A. External therapeutic use of radioactive phosphorus; erythema studies. *Radiology*, 1946, *47*, 213–222.

* For discussion see page 30.

THE DEPOSITION OF RADIOACTIVE METALS IN BONE AS A POTENTIAL HEALTH HAZARD*†

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THE radioactive elements involved in nuclear fission present a danger to those working in production plants and laboratories handling this material. Many of these elements are deposited in the skeleton where they constitute a hazard quite similar to that of chronic radium poisoning. During the 1920's several hundred persons died from the effects of radium exposure. Many of these individuals had worked in the luminous dial plants in World War I. The effects of chronic radium poisoning, which include osteomyelitis, bone necrosis and osteogenic sarcoma, were referable to the chronic radiations from minute doses of radium which had been deposited in the skeleton. When a nuclear chain reaction pile became a probability, it was recognized that the amounts of radioactive materials involved would be many million times greater than anything encountered in the radium industry.

In general, the radioactive isotopes produced in the fission process have short half-lives, so that radioactive decay quickly reduces their concentration. However, certain isotopes, including those of strontium, yttrium, cerium, and plutonium, have such long half-lives that they would present a serious hazard of chronic radiation toxicity should an individual become contaminated. These elements are rapidly fixed in the skeleton, and are eliminated at a very slow rate. The localization of these elements in the skeleton exposes the sensitive cells of the bone and bone marrow to toxic radiations, with the resulting danger of bone marrow destruction, bone necrosis and bone tumors.

The metabolism of bone was investigated to determine the factors concerned in the absorption and deposition of these elements in the skeleton and the precise sites of localization. The chronic elimination of these radioactive materials was studied in rats, and the effects of the standard procedures used in treating chronic radium poisoning were compared. Finally, a possible mechanism for reducing the toxicity of the plutonium deposits in the bone was investigated.

The first element studied was radioactive strontium (Sr*). This alkaline earth closely resembles calcium in behavior[1] and thus serves as an indicator for calcification activity and calcium metabolism. It was the only element in the group to be absorbed to any significant extent from the intestinal tract, and so presented a potential danger from contaminated food or water.

Only two factors were found to have a marked effect on the absorption of Sr* from the gut. These were: (1) the age of the animals, and (2) the adequacy of calcium in the diet (Table 1).

When a given dose of Sr* was fed to young, growing rats on a diet low in calcium the skeletal retention was almost twenty-five times as great as that of adult rats on a

* The symbols Sr*, Y*, Ce*, or Pu* indicate the respective element "labelled" by its content of radioactive isotope.

* This document is based on work performed under Contract No. W-7405-eng-48-A for the Manhattan Project, and the information covered in this document will appear in Division IV of the Manhattan Project Technical Series, as part of the contribution of the Radiation Laboratory, University of California.

† Presented at the Twenty-eighth Annual Meeting, American Radium Society, San Francisco, Calif., June 28–29, 1946.

high calcium diet (Table I). Although not so marked, the same general effect was noted (Table II) when the Sr* was injected intraperitoneally; young calcium deficient rats retained almost four times as much Sr* in the skeleton as did adult animals on a high calcium diet, reflecting the increased calcification activity in the former.

These results indicate an increased hazard from radioactive strontium, and presumably radium, to young, growing individuals and to those on a low calcium diet. Accordingly, work involving exposure to radio-strontium or radium should be restricted to adults, and care should be taken to maintain a high level of calcium intake in these individuals.

In contrast to strontium, no significant difference in the behavior of plutonium, yttrium, or cerium was observed when these same two groups of animals were compared (Table II).

Another condition which profoundly influences bone metabolism is severe phosphorus deficiency, first reported in rats by Day and McCollum[2] in 1939. When young rats were placed on a diet containing less than 0.01 per cent phosphorus, severe deficiency signs appeared within two weeks including marked demineralization of the skeleton. The bones contained only one-fourth of the bone salt present in the skeleton of normal control rats. It has been suggested that this demineralization is due

TABLE I

EFFECT OF SKELETAL GROWTH AND CALCIUM INTAKE ON THE ABSORPTION OF Sr* FROM THE GUT

Age	Diet (2 months)	Per Cent of Dose of Sr* in		
		Carcass	Feces	Urine
Young, growing	Low calcium	73.1	20.9	2.7
Young, growing	High calcium	17.1	58.8	13.3
Old, adult	Low calcium	15.7	69.9	8.4
Old, adult	High calcium	2.8	81.8	8.3

(Figures given are the averages for the 5 animals in each group.)

TABLE II

EFFECT OF AGE AND CALCIUM DEFICIENCY ON Sr*, Pu*, Y*, AND Ce*

Element	Age	Diet	Per Cent of Dose Absorbed	Per Cent of Absorbed Dose in			
				Carcass	Urine	Feces	Liver
Sr*	Young	Ca deficient	100	70.3	1.8	22.0	
	Old	High calcium	100	14.1	41.7	29.2	
Pu*	Young	Ca deficient	46.0	71.4	3.3	6.5	10.4
	Old	High calcium	48.9	63.2	4.3	13.5	12.9
Y*	Young	Ca deficient	77.0	80.9	7.2	7.6	4.3
	Old	High calcium	77.4	77.1	14.3	5.2	3.4
Ce*	Young	Ca deficient	89.2	51.8	1.1	7.1	40.0
	Old	High calcium	85.5	34.4	9.8	17.2	38.6

(The figures given are average values for each group of 5 rats. Sr* was injected intraperitoneally, Pu*, Ce*, Y*, intramuscularly.)

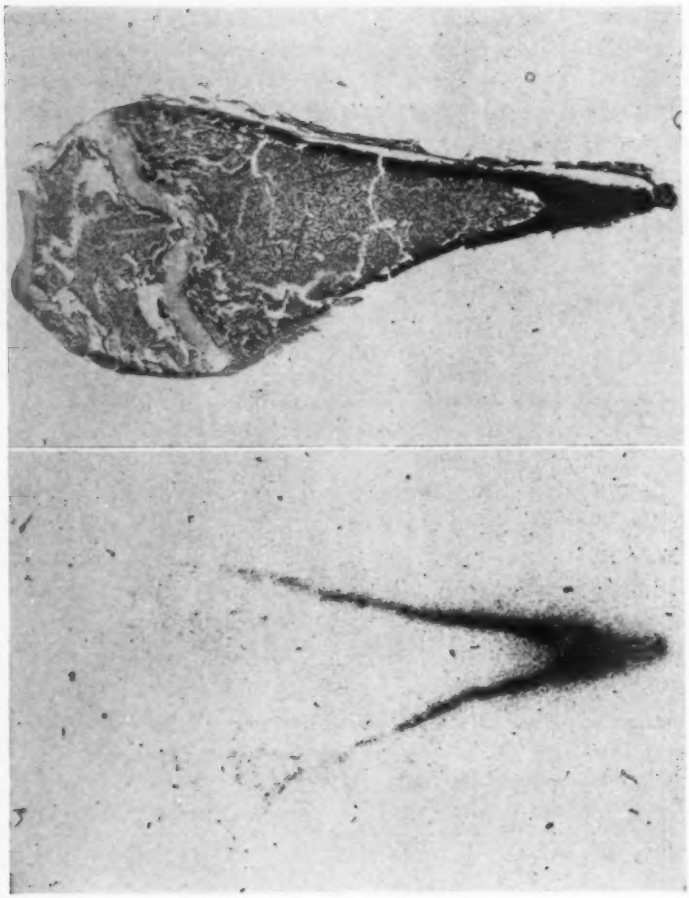

FIG. 1. Femur from rat weaned to phosphorus deficient diet at three weeks, injected intraperitoneally with 5 microcuries of strontium at five weeks, and sacrificed one week later. Note that the strontium is deposited almost exclusively in the bone salt of the shaft, with practically none in the uncalcifiedo steoid matrix below the epiphysis. (Hematoxylin, eosin, and silver nitrate) (×13).

TABLE III

EFFECT OF PHOSPHORUS DEFICIENCY ON RETENTION OF Sr*, Pu*, Y*, AND Ce*

Element	Diet	Per Cent of Dose Absorbed	Per Cent of Absorbed Dose in		
			Carcass	Urine	Feces
Sr*	Control	100	76.3	5.6	8.3
	P deficient	100	25.8	36.5	12.7
Pu*	Control	30.3	80.1	2.8	6.0
	P deficient	58.0	83.9	3.7	6.8
Y*	Control	57.9	75.7	12.7	5.4
	P deficient	64.5	74.1	8.4	11.5
Ce*	Control	85.0	60.5	5.7	12.0
	P deficient	89.0	71.9	4.8	5.0

(Sr* injected intraperitoneally, Pu*, Y*, and Ce* injected intramuscularly.)

to a resorption of bone salt to replace the phosphorus lost in the excreta, in order to provide phosphorus for the essential needs of the soft tissues. In agreement with this view, it was found that the retention of Sr* was greatly reduced in the phosphorus deficient animals (Table III). However, no significant effect on the retention of Pu*, Y*, or Ce* was observed.

Phosphorus-deficient animals were injected with radioactive elements, and were sacrificed four days later. The bones were removed, and radio-autographs were prepared. The latter was accomplished by exposing no-screen x-ray film to 10 micron sections of undecalcified bone sections until darkening of the film took place, the film darkening indicating the site of deposition of the radioactive materials. Owing to the extreme demineralization of

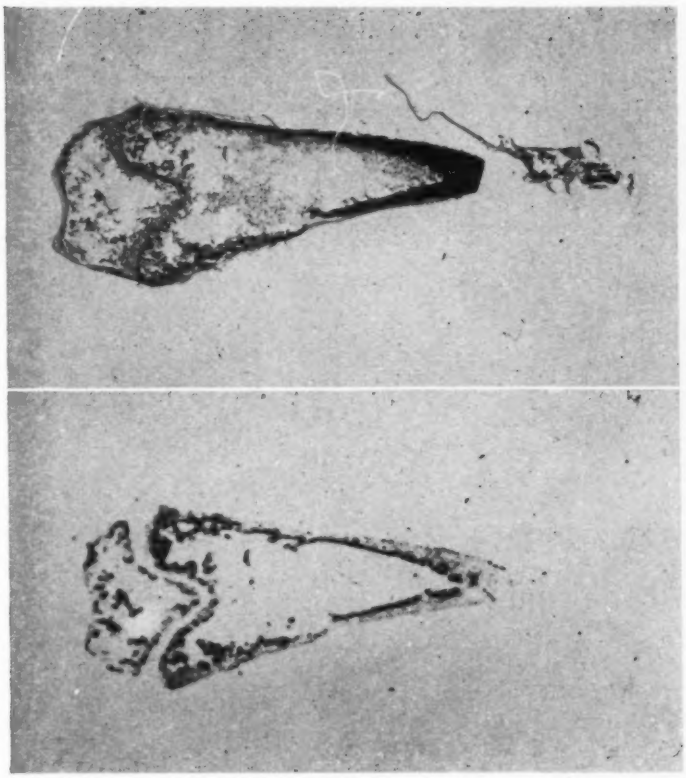

FIG. 2. Femur from rat weaned to phosphorus deficient diet at three weeks, injected intramuscularly with 20 micrograms plutonium at five weeks, and sacrificed at six weeks. Note heavy deposits of plutonium in the uncalcified osteoid matrix below the epiphysis, and superficial deposition of plutonium in the shaft. (Hematoxylin, eosin, and silver nitrate) (×7½).

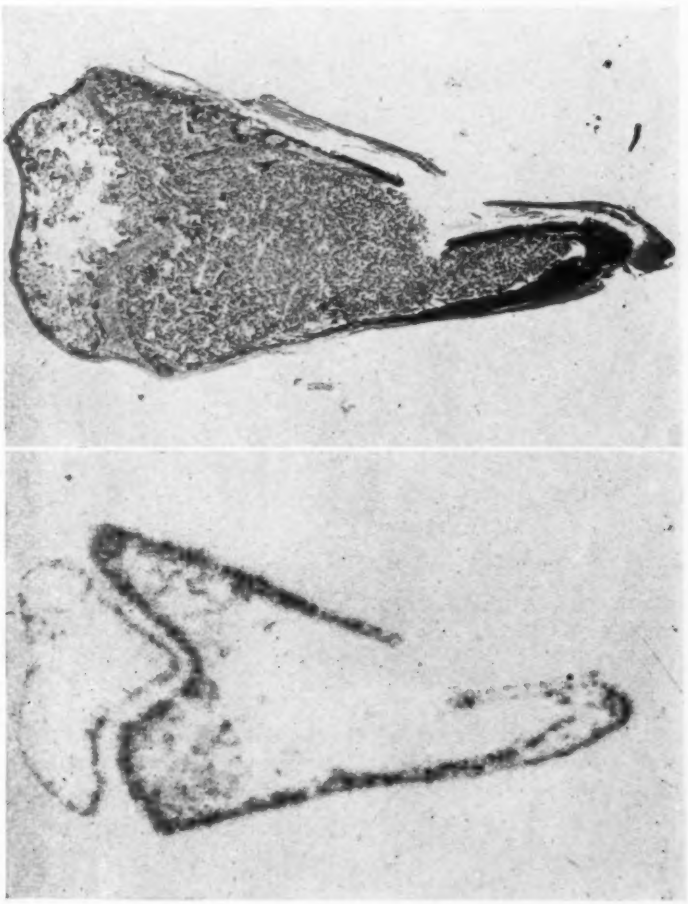

FIG. 3. Femur from rat weaned at three weeks to the phosphorus deficient diet, injected intramuscularly with 2.5 microcuries of yttrium at five weeks, and sacrificed one week later. Note superficial deposition of yttrium in the shaft, and heavy deposits in the uncalcified osteoid matrix below the epiphysis. (Hematoxylin, eosin, and silver nitrate) (×17).

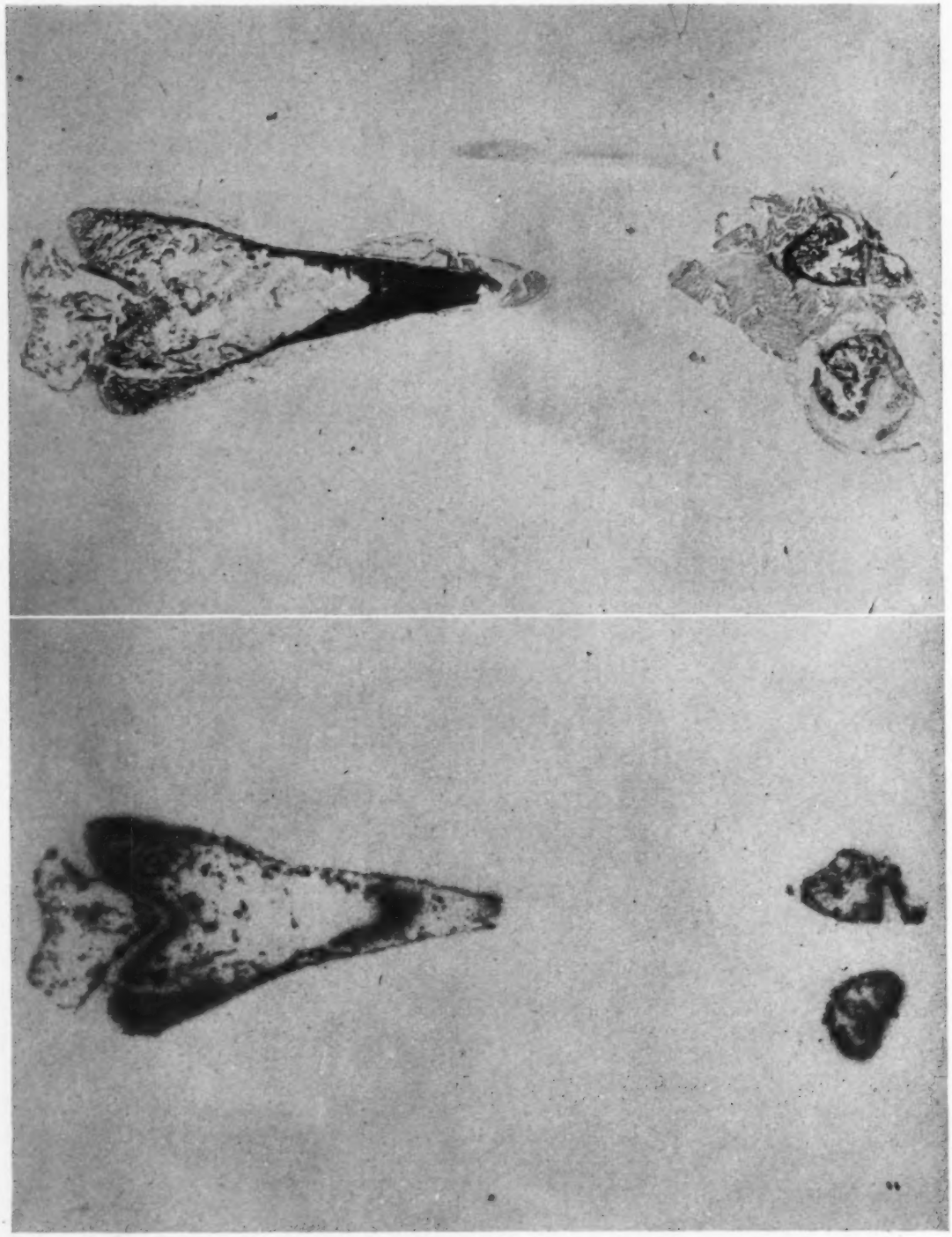

FIG. 4. Femur from rat weaned to phosphorus deficient diet, injected intramuscularly with 2.5 microcuries cerium at five weeks, and sacrificed one week later. Note the superficial deposition of cerium in the shaft, the heavy deposits in the uncalcified osteoid matrix below the epiphysis, and scattered points of radioactivity within the shaft. (Hematoxylin, eosin, and silver nitrate) (×8).

the skeleton of these animals, large areas of the bone consisted of uncalcified organic matrix, free from bone salt. The radio-autograph for Sr* (Fig. 1) shows that this element was deposited only in the thin shell of bone salt remaining in the shaft. Plutonium (Fig. 2), on the other hand, was actively laid down in the uncalcified organic bone matrix below the epiphyseal cartilage and in the endosteum and periosteum. None was deposited in the cartilage itself. Yttrium (Fig. 3) was deposited superficially in the shaft with heavy deposits in the uncalcified osteoid matrix below the epiphyseal cartilage. Similarly, cerium (Fig. 4) was deposited superficially in the shaft, with scattered points of radioactivity within the shaft, and heavy deposits in the uncalcified osteoid matrix below the epiphyseal cartilage.

Thus, a fundamental difference in the behavior of Sr* as compared with Pu*, Ce*, and Y*, was indicated by the radio-autographic and metabolic studies. Sr* appeared to follow the path of calcium metabolism and was deposited only in the bone salt; Pu*, Y*, and Ce* were laid down in the uncalcified organic matrix of bone and appeared to be unrelated to calcium in behavior. This is in sharp contrast to the generally accepted view with regard to the behavior of other heavy metals which deposit in the skeleton.

After the material has localized in the skeleton, the major problem is one of excretion. The curves in Figure 5 show the residue of the radioactive dose in the body plotted against time. By using semilogarithm paper, curves analogous to radioactive decay curves are obtained which give a measure of the biological half-life of each element in the body. They also indicate the relative stability of each element and show some of the features of elimination. Sr* appeared to be eliminated more readily than the other elements, with a biological half-life of only three to four months. Pu* Y*, and Ce* were excreted very slowly and the biological half-lives of these elements ranged from one to three years.

Treatments advocated in chronic radium poisoning[3] were investigated to determine their effect on the chronic elimination of these elements. The procedures, such as low calcium diet, parathormone, ammonium chloride and citrate, were all designed to cause some bone resorption and increased

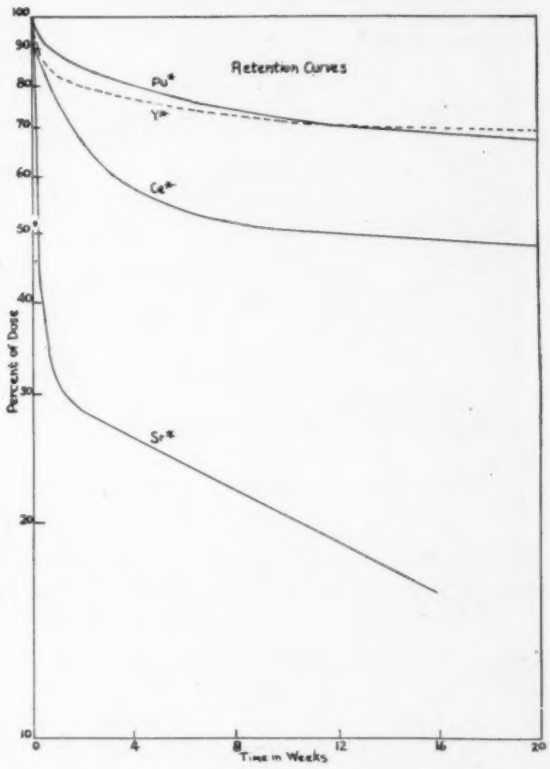

Fig. 5

excretion of calcium. They had no significant effect on the excretion of Pu*, Y*, or Ce*, and although they did cause a small increase in the excretion of Sr*, it was still at too slow a rate to have any appreciable effect on the residue left in the body.

Since it did not appear feasible to remove the plutonium from the body by such means, some other method of reducing its toxicity in bone was sought. Radio-autographs showed that Pu* was deposited on the surface of the bone and bone trabeculae, so that the radiations were concentrated on the cells of the endosteum, periosteum, and bone marrow, which might account for the high relative toxicity of plutonium. Since

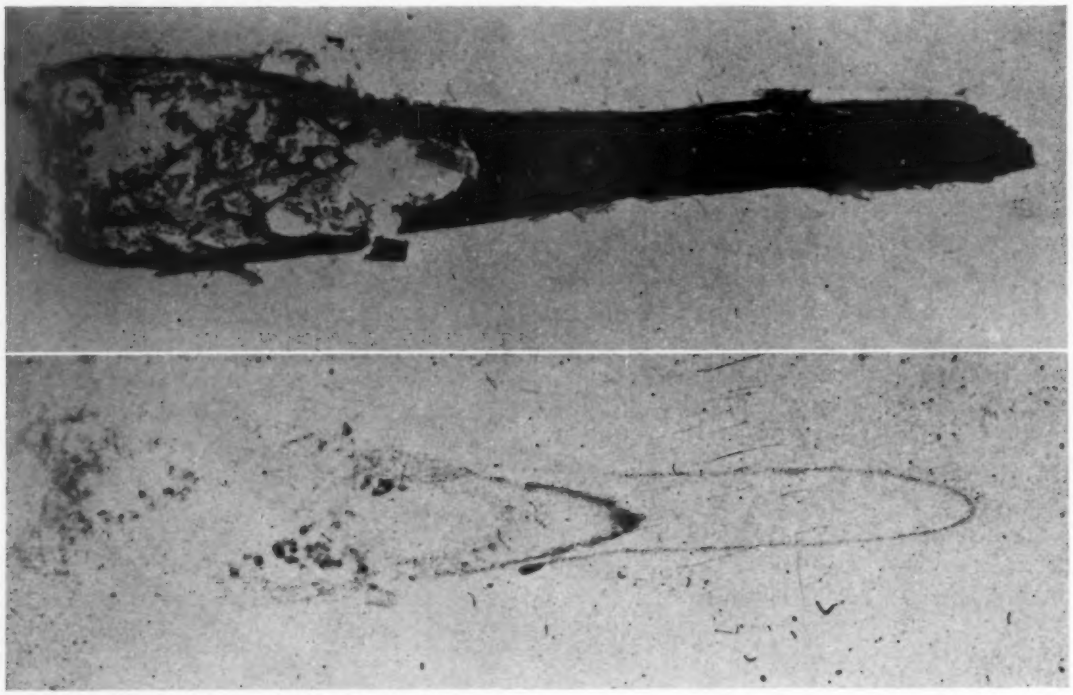

FIG. 6. Femur from an adult male rat which was injected intramuscularly with 25 micrograms of plutonium. Six weeks after injection the leg with the unabsorbed plutonium was amputated. After another six weeks, it was put on a diet deficient in calcium and phosphorus containing 2 per cent aluminum sulfate. After six weeks on this demineralizing diet it was changed to the stock diet supplemented with 2 per cent dicalcium phosphate and 2 per cent cod liver oil. It was sacrificed six weeks later. Note the linear plutonium deposit buried deep in the shaft, and the light plutonium activity in the bone laid down on top of it. Some of the trabeculae still contain plutonium, while others, possibly formed during regeneration, are free of plutonium. (Hematoxylin, eosin, and silver nitrate) (×6½).

these deposits of Pu* remain fixed, and since the range of the alpha particles is short, it was felt that by laying down new, non-radioactive bone on top of the Pu* deposits, the short range radiations could be prevented from reaching the living cells. This was accomplished by placing rats which had been injected with plutonium for one month on a regimen designed to produce bone resorption, and then changing them to an optimum diet calculated to restore the bones with new non-radioactive bone. The results of this procedure are shown in the radio-autograph in Figure 6, in which the dense deposit of plutonium is buried deep in the shaft. This may provide a means for reducing the toxicity of plutonium in bone. It has not been as yet possible to test this method by actual toxicity studies in animals.

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For discussion see page 30.

VOL. 58, NO. 1

RETENTION OF RADIOACTIVE IODINE IN THYROID CARCINOMAS

HISTOPATHOLOGIC AND RADIO-AUTOGRAPHIC STUDIES*

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IN 1938 it was shown by Hertz, Roberts and Evans[6] that the mammalian thyroid was capable of selectively accumulating radioactive iodine following its intravenous injection as aqueous sodium iodide. In 1939 Hamilton and Soley[2] studied the uptake of radioactive iodine by the human thyroid. They reported[5] on a series of 40 patients, in 2 of whom there was thyroid carcinoma. In these 2 patients the cancerous thyroid tissue picked up only about 1 per cent as much of the radioactive material per gram as did the non-cancerous thyroid tissue. In later studies Hamilton and others[3,4,5] were able to trace the anatomical localization of radioactive iodine in human thyroid tissue and in cancers of that organ by utilizing the technique of radio-autography, a method originally devised by Lacassagne and Lattes[7] in 1924.

PRESENT STUDY

During the past three years at Memorial Hospital tissue sections and radio-autographs from 19 cases of thyroid carcinoma have been prepared and studied. Included in this group are 4 cases which were generously made available by Dr. Seidlin of Montefiore Hospital and Dr. Keston of Bellevue Hospital. Several of the 19 cases had received large therapeutic doses of the eight day isotope (I^{131}) but the large majority had received tracer doses ranging from 500 to 1,500 microcuries. The amount of inactive iodine was usually 0.05 to 0.1 mg. The objectives of this physical and histopathologic investigation were (1) to ascertain which of the various types of thyroid carcinoma possessed the ability to retain the radioactive material; (2) to determine whether structural types were an important or minor influence in the ability of the tumors to pick up the isotope, and (3) to gain information as to whether this means of physiologic irradiation could be expected to achieve a palliative or curative influence in cases of thyroid carcinoma.

PREPARATION OF RADIO-AUTOGRAPHS

The technique of radio-autography as employed in the cases reported here is a simple one and may be described briefly as follows. Tracer or therapeutic doses of radioactive iodine as sodium iodide in water solution are administered to the patient by mouth. Within twenty-four to forty-eight hours the anticipated surgical procedure is carried out. Blocks of tissue about 2–3 mm. in thickness are fixed in 10 per cent formalin. Wherever possible, blocks of non-cancerous thyroid are included and sufficient blocks are prepared from both the cancerous and non-cancerous tissue to insure that sections will be secured representing a complete picture of structural features present. The tissue blocks are dehydrated in dioxan and impregnated with paraffin. Thin sections are cut with a microtome and these are dried in an oven or over a flame. These procedures can be carried out with satisfactory results within the space of three to four hours. After the sections are dried the paraffin is removed by passing the sections through several changes of fresh xylene. The exposed surfaces of the de-paraffinized sections are then placed directly against the emulsion surface of a photographic plate or roentgen film. Brass

* Presented at the Twenty-eighth Annual Meeting, American Radium Society, San Francisco, Calif., June 28–29, 1946.

weights maintain the sections in accurate position and they are exposed for varying periods of time depending upon the degree of radioactivity present. In this connection it has been found useful to make preliminary measurements of activity with a Geiger counter. Those sections which show little or no activity are exposed for as long as three weeks. At the end of the exposure interval the plates are developed and the sections are stained with hematoxylin and eosin. Areas of darkening on the photographic plate or film map out the distribution pattern of the radioactive material in the sections under scrutiny. This pattern can be effectively studied by comparing it with the stained tissue section by means of low power microscopy. It has been our practice to cut sections in quadruplicate and to make exposures from each of the four sections. This serves as a useful control and check over artefacts. This practice of multiple controls has well demonstrated the reliability of the method inasmuch as there is practically no variation in the patterns recorded on the various plates. Where variations do occur they can almost invariably be checked and explained by comparing the radio-autograph with the appropriate stained section.

In the process of preparing the sections for radio-autography the minute amount of the radioactive material lost in the solutions is of no significance. Frozen section technique alone or combined with paraffin technique was used in a few of the earlier cases. The freezing technique was found to be distinctly inferior to the paraffin method and was soon abandoned. The disadvantages of frozen sections include the undesirable qualities of thickness, the difficulty of securing entirely flat preparations and the unavoidable loss of colloid when the sections are manipulated in solutions. It cannot be expected that the paraffin technique entirely prevents the loss of some of the follicular colloid but it is distinctly diminished when compared with the results from frozen sections. The loss of colloid could probably be further diminished by utilizing celloidin technique.

Study of the histologic distribution of the radioactive material can be greatly facilitated by the preparation of prints or transparencies enlarged from 10 to 20 diameters. Corresponding magnifications of the tissue sections are made for purposes of comparison. In our material it must be stated that the radio-autographs do not furnish an accurate cell by cell distribution of the retained isotope but one may successfully interpret the pattern as reflected by aggregate cell groups or large collections of colloid. The inability to orient structure and function in more minute detail is admittedly a handicap. For example, it is often not possible to be certain whether there is a greater accumulation of the isotope in acinar colloid or in adjacent epithelium. One may, however, ascertain this frequently enough for many determinations. When this can be done, it is necessary to have structural contrasts that are somewhat isolated so that they can be dissociated from the more diffuse and denser areas on the photographic plate. We have been unable to detect any deposition of the radioactive material in connective tissues and have found its deposit limited to epithelium and colloid. The failure to secure more accurate patterns is due to the fogging of structural margins caused by the diffusion and scattering of the longer range beta rays.[1,3]

CLASSIFICATION OF THYROID CARCINOMAS

Before presenting the histopathologic and radio-autographic findings in the 19 cases previously referred to, it seems necessary to illustrate and to comment briefly upon the various structural types of thyroid carcinoma and to point out the pleomorphism exhibited by this group of tumors when viewed collectively as well as individually. In Table 1 is a list of histpathologic types of thyroid carcinomas, for which no originality is claimed. In the right hand column is an expression of the relative frequency of each type.

Papillary Adenocarcinoma. Fortunately

this is the most frequent form of thyroid carcinoma and the group yielding the most satisfactory clinical results. Characteristically the tumors are of a low order of malignancy. Figure 1 shows a coarsely papillary thyroid carcinoma containing characteristic dark round calcific concretions usually referred to as psammoma bodies. In Figure 2 is another structural type of papillary thyroid carcinoma made up of rather orderly cuboidal and columnar cells arranged usually in a single row along delicately vascularized connective tissue cords containing very little stroma. In both Figures 1 and 2 the lack of true gland formation and the absence of colloid should be noted. These papillary tumors have a tendency to occur in young individuals, but they are well known in the later decades of life. It is the only form of thyroid carcinoma familiar to us as showing rather uniformly at least a moderate degree of sensitivity to roentgen rays. Fatal cases of this disease are quite apt to run a very prolonged clinical course often covering a number of years.

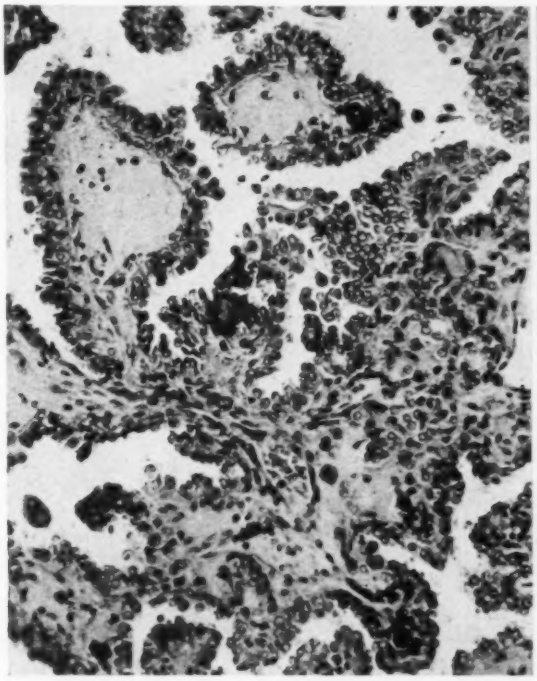

FIG. 1

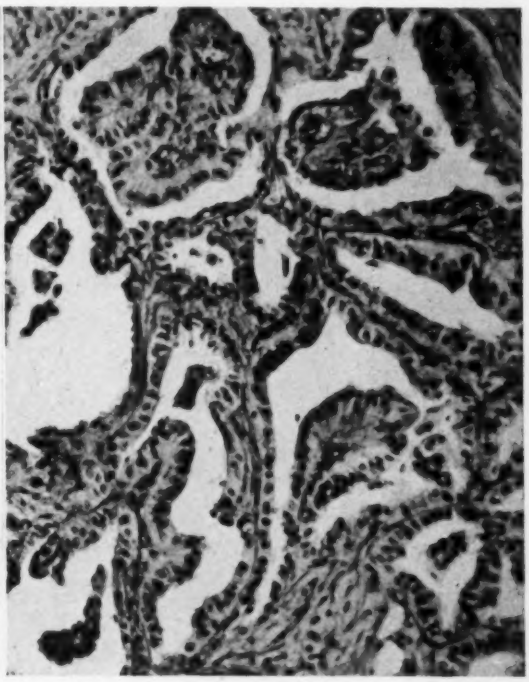

FIG. 2

Follicular and Alveolar Adenocarcinoma. The term follicular as used here implies the reproduction in a thyroid tumor of structures having some resemblance to thyroid follicles. Hence it is used in a descriptive and not a derivative sense since the thyroid follicles for practical purposes are the ultimate source of all thyroid carcinomas. The term alveolar as herein employed refers to a structural arrangement less differentiated than the previously used term, follicular, and moreover one can refer to open alveolar where there is lumen forma-

TABLE I

CLASSIFICATION OF THYROID CARCINOMA

	Per Cent
Papillary adenocarcinoma	40
Follicular and alveolar adenocarcinoma	20
Solid alveolar adenocarcinoma	25
Anaplastic carcinoma	2
Hurthle cell adenocarcinoma	5
Spindle and giant cell carcinoma	5
Metastasizing struma	3

tion or solid alveolar where cellular proliferation has left no residual lumen. In Figure 3 is an illustration of a follicular and alveolar adenocarcinoma. Here and there are follicle-like structures which contain pink-staining material having the appearance of colloid. There is considerable variation in the contour and cellularity of the follicular groups and in some areas alveolar formations with and without lumina are present. Thyroid tumors exhibiting the structural qualities seen in Figure 3 are distinctly more clinically malignant than the papillary group previously discussed.

FIG. 3

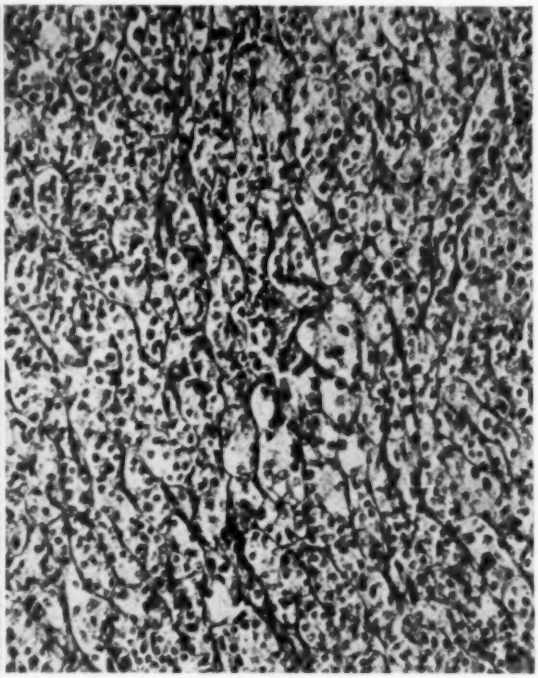

FIG. 4

Solid Alveolar Adenocarcinoma. This group could easily be merged with the preceding group but is discussed separately here inasmuch as a certain significant number of thyroid adenocarcinomas are almost exclusively solid alveolar in structure. In Figure 4 is shown a very cellular solid alveolar tumor with much nuclear variation as to size and depth of staining. Note that no colloid is present since there are no lumina. This is a tumor of quite high grade malignancy and the rate of cure is very low.

Solid Anaplastic Thyroid Carcinoma. This constitutes a small group of thyroid carcinomas in which near total or total lack of differentiation is seen. In Figure 5 is such a tumor with a structural pattern so indifferent that it simulates the histopathologic traits of lymphosarcoma. Indeed, on some occasions the anaplasia is so marked that one finds it difficult to separate this tumor from lymphosarcoma. Unless some alveolar grouping of cells or other epithelial qualities are demonstrable in these cases definite diagnosis cannot be made. As might be expected cure in such cases is a great rarity.

Hurthle Cell Adenocarcinoma. This is one of the most characteristic histopathologic forms of thyroid carcinoma and is featured by the presence of bright pink-staining cells. This tinctorial quality is confined to the cytoplasm which is usually abundant and rather opaque. Most commonly the cell type concerned is columnar and the cells

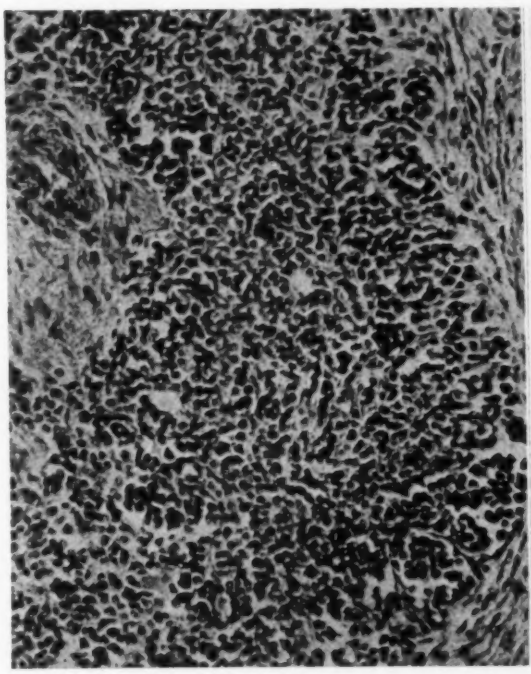

Fig. 5

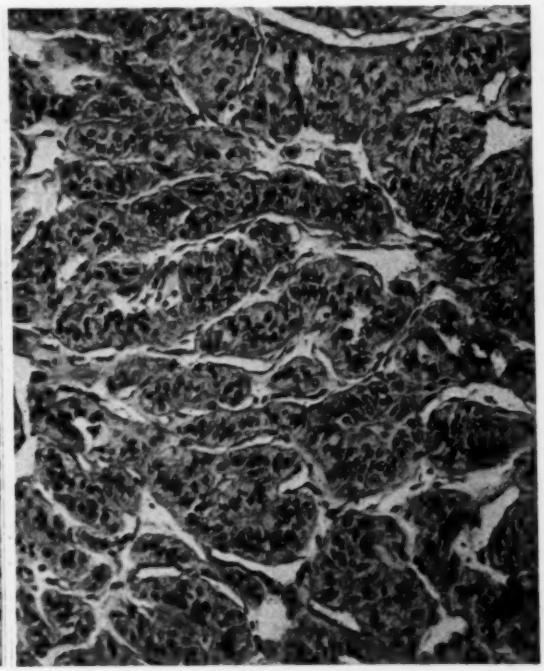

Fig. 6

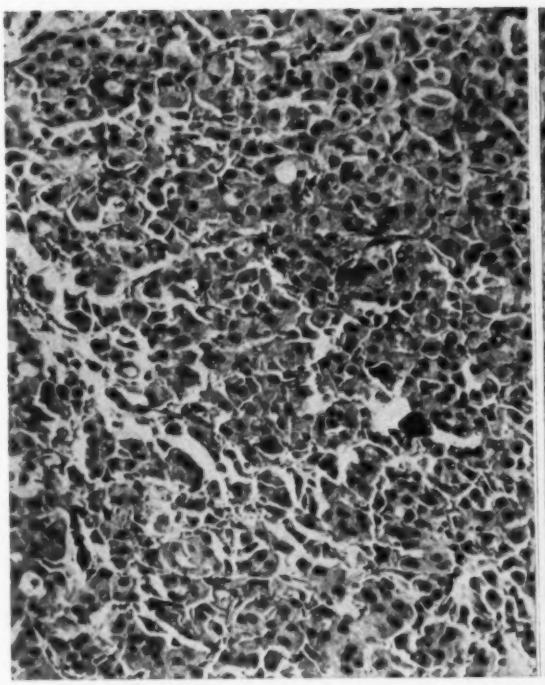

Fig. 7

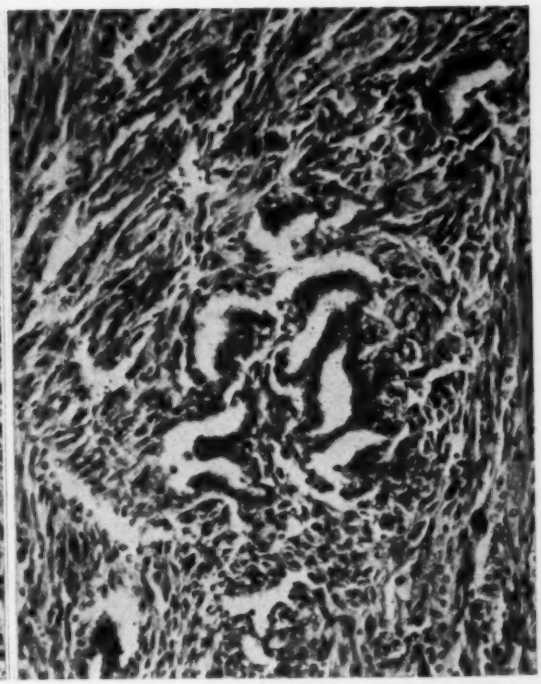

Fig. 8

tend to be stratified in plexiform groups separated commonly by a rich thin-walled capillary blood supply. Such a tumor is shown in Figure 6. In Figure 7 is a less common form of Hurthle cell adenocarcinoma, more diffuse and made up of more rounded

and polygonal cells somewhat similar in shape to hepatic cells. Generally speaking, Hurthle cell carcinomas tend to metastasize late and to run a prolonged clinical course, exceptional cases surviving for many years. The less differentiated Hurthle cell carcinomas, few in number, are capable of early metastatic dissemination.

Spindle and Giant Cell Carcinoma. A dual descriptive designation is given to this group since a certain small number of highly malignant thyroid carcinomas are characterized by the presence of both spindle and giant cells. There are members of this group which are predominantly spindle cell and others that are chiefly giant cell. If one preferred, separate listings could be made for these tumors in which there is a predominating structural component. Figure 8 represents an area from a thyroid carcinoma principally spindle cell in make-up. Here and there, however, are a few residual areas of atypical gland formation. In Figure 9 is a highly anaplastic thyroid carcinoma made up of quite large indifferently arranged giant epithelial cells. In thyroid cancers studied by us, spindle and giant cell carcinoma is the most malignant single neoplasm of this organ. We do not have in our records a single cure of this form of the disease.

Benign Metastasizing Struma. This term refers to a rare form of thyroid tumor characterized by the ability to yield metastatic growths in distant foci while maintaining a peculiarly benign histopathologic appearance. The term, benign, used in reference to this peculiar tumor is a structural and not a clinical designation. It is admittedly defective inasmuch as all component parts of a tumor classified as benign metastasizing struma may not be strictly benign in aspect. The more material one studies from cases classified in this group, the more impressed he is with the presence in both primary and metastatic lesions of areas having the morphologic aspect of fully malignant thyroid carcinoma. Multiple sectioning is often necessary to develop these qualities but when looked for they become more the rule than the exception. In Figure 10 is pictured an example of

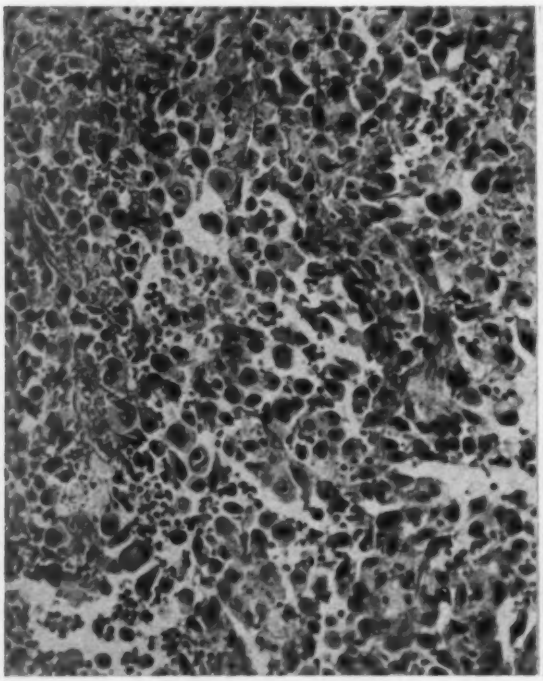

FIG. 9

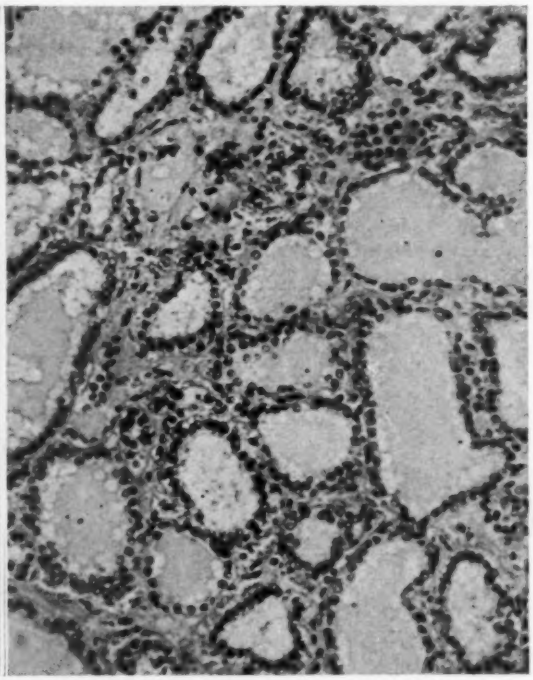

FIG. 10

Fig. 11

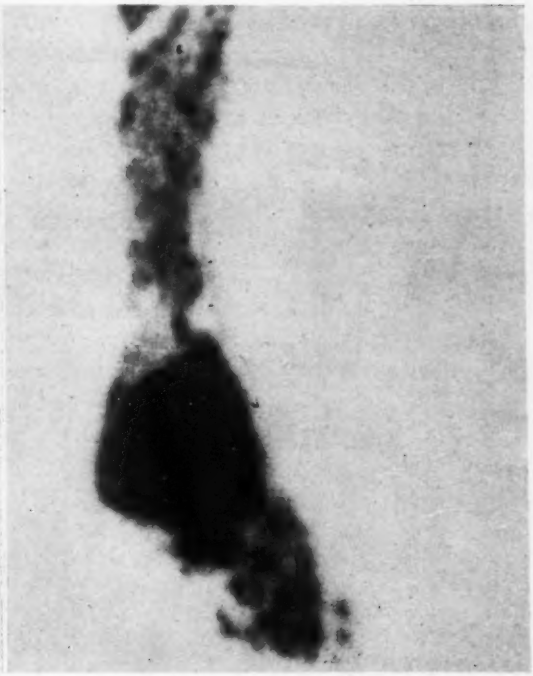

Fig. 12

so-called benign metastasizing struma. The photomicrograph was made from a lung metastasis. Observe the uniform follicular structure and the abundantly distributed colloid.

Figures 1 through 10 should serve to illustrate the broad range of histopathologic structure that is encountered in thyroid carcinomas as a group. Actually the range of structural variation in these tumors is much greater than can be shown in a limited number of photomicrographs. It must be understood that the foregoing classification scheme is by necessity more explicit than is actually the case. Thyroid cancers are seldom pure and homogeneous in their microscopic make-up. Often there is interplay between papillary and follicular structure or an intermixing of follicular and solid alveolar areas. Hence in making any classification scheme it is necessary to classify on the basis of dominant structural traits or to use a complicated terminology sufficient to designate multiple structural traits. For these reasons any classification of thyroid carcinomas must be partially defective. In making routine diagnoses of thyroid carcinomas our practice has been to report the various structural features present and to give some numerical estimate on a basis of one to four as to the degree of malignancy. In certain extreme cases of thyroid cancer a single tumor may contain almost every structural type listed in the preceding classification scheme. Perhaps the purest histopathologic type is the Hurthle cell carcinoma. In regard to so-called benign metastasizing struma, homogeneity of structure becomes less outstanding when one is able to examine multiple blocks from a given tumor site or blocks representing multiple metastatic foci. The structural variations discussed have an important bearing on the ability of thyroid tumors to pick up radioactive iodine, as will be seen in the following.

CORRELATION OF RADIO-AUTOGRAPHIC AND HISTOPATHOLOGIC FINDINGS

It is scarcely surprising to find that a group of neoplasms of such diverse histo-

pathologic make-up differ in their ability to retain radioactive iodine. The illustrations that follow will serve to establish this point of view. The illustrations are shown in pairs and the left panel will represent the tissue section, the right panel the corresponding radio-autograph. Each tissue radio-autographic pair is reproduced at identical magnification.

In Figure 11 is a section of a low grade papilllary adenocarcinoma. The tumor is clearly demarcated from adjacent non-cancerous thyroid tissue. This section of tumor is unusually homogeneous, being papillary throughout. In Figure 12 is the corresponding radio-autograph which demonstrates that the areas of darkening outline the non-cancerous thyroid tissue. There is absolutely no darkening of the plate where it was in contact with the tumor itself. At the lower left of Figure 11 is an oval area which histologically represents an inactive-looking adenomatoid nodule rich in colloid. In Figure 12 this oval area is shown to have picked up a relatively large amount of isotope as judged by the degree of darkening caused by other thyroid tissue present. Detail is insufficiently shown to enable one to state whether the colloid or the epithelium in this adenomatoid nodule is the site of principal storage.

A section of another primary tumor is shown in Figure 13. The tumor is composed of both papillary and follicular elements. The upper two-thirds of the left border of the tissue section is made up of purely papillary tumor. The radio-autograph in Figure 14 reveals no darkening that corresponds with this area of purely papillary tumor. In the lower half of Figure 13 are four rounded nodules and there is a fifth similar nodule at the upper right of the section. These nodular areas represent low grade thyroid adenocarcinoma combining both papillary and follicular qualities. If one compares the degree of darkening that these areas have produced on the radio-autograph it becomes apparent that the retention of the isotope is not entirely uniform. From nodule to nodule the rela-

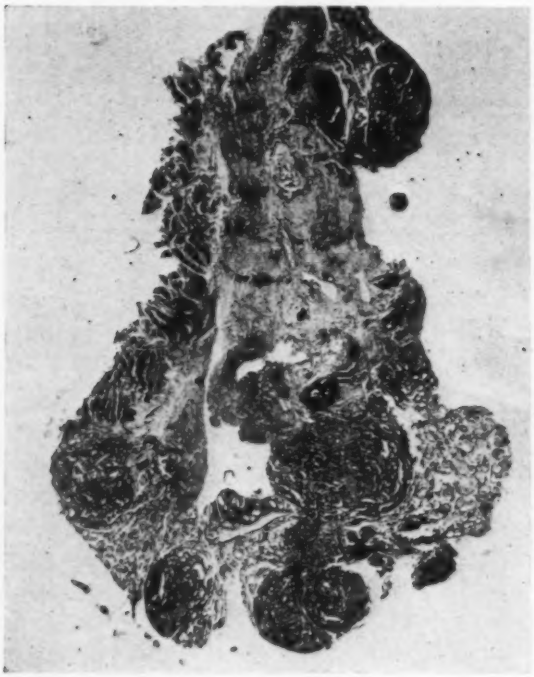

FIG. 13

FIG. 14

tive amount of papillary tissue as opposed to follicular tissue is more nearly equal than is the degree of darkening that these nodules have produced in Figure 14. This statement is based on similar patterns in quadruplicate sections and radio-autographs.

Figure 15 represents three adjacent lymph node metastases of papillary and follicular thyroid adenocarcinoma. Somewhat the same situation is present in Figures 15 and 16 as seen in Figures 13 and 14, namely that here are examples of essentially similarly constituted tumors having a distinctly different ability to retain the radioactive isotope. The larger node section in Figure 15 exhibits a fairly satisfastory pick-up pattern but the tumor tissue in the upper smaller nodes is almost totally non-functional. That this is not due to artefact is revealed by repetition of these findings in quadruplicate sections and radio-autographs. Under ordinary circumstances there is much closer correlation between structure and pick-up pattern than shown in the last two cases. They are presented as exceptions rather than the rule.

An orderly follicular thyroid adeno carcinoma is seen in Figure 17. The corresponding radio-autograph of Figure 18 gives evidence of uniform retention of the administered isotope.

Another orderly follicular carcinoma with a rim of adjacent thyroid tissue is illustrated in Figure 19. Study of the corresponding radio-autograph in Figure 20 reveals a relatively low pick-up in the tumor as contrasted with the pick-up pattern of the noncancerous thyroid tissue seen in the lower left hand corner.

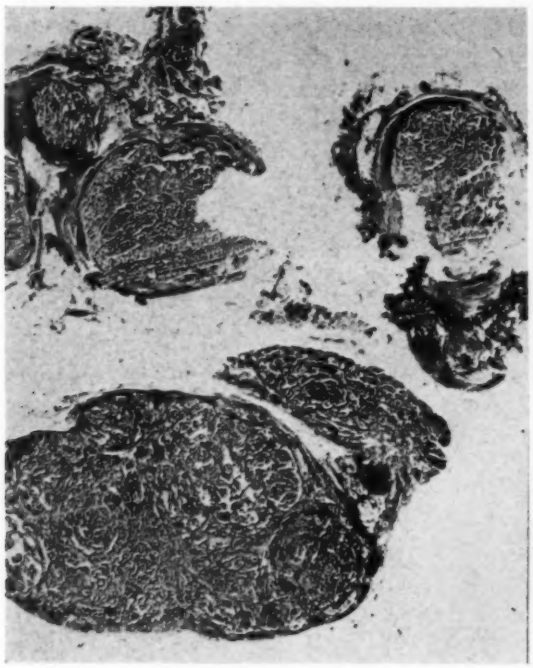

Fig. 15

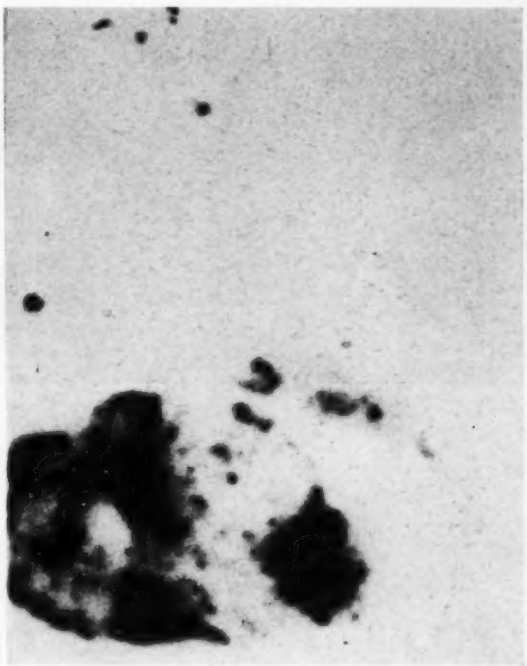

Fig. 16

In the cases so far studied we haved found no example of thyroid carcinoma of high-grade malignancy that demonstrated the retention of radioactive iodine with one exception. This is shown in Figure 21 which is a medium magnification of a solid alveolar adenocarcinoma; in Figure 22 is the corresponding radio-autograph. The section was taken from a lymph node metastasis. The possibility of artefact was

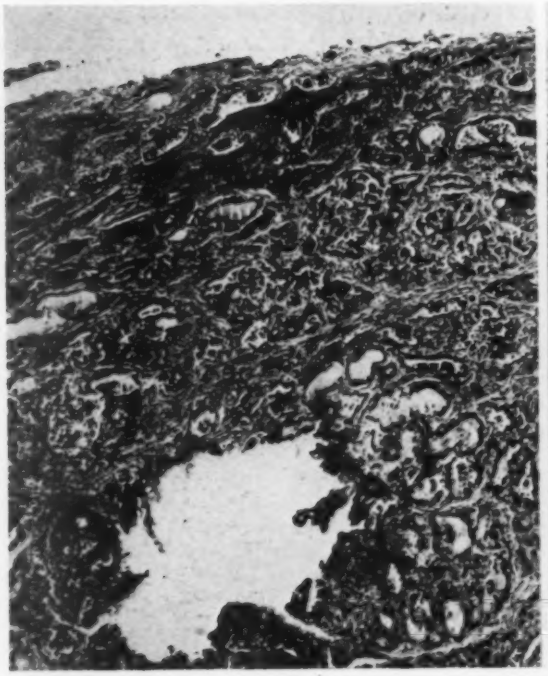

Fig. 17

Fig. 18

Fig. 19

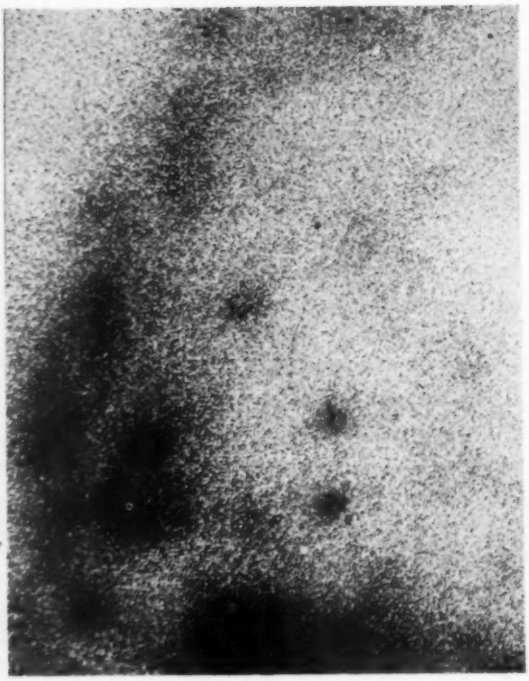

Fig. 20

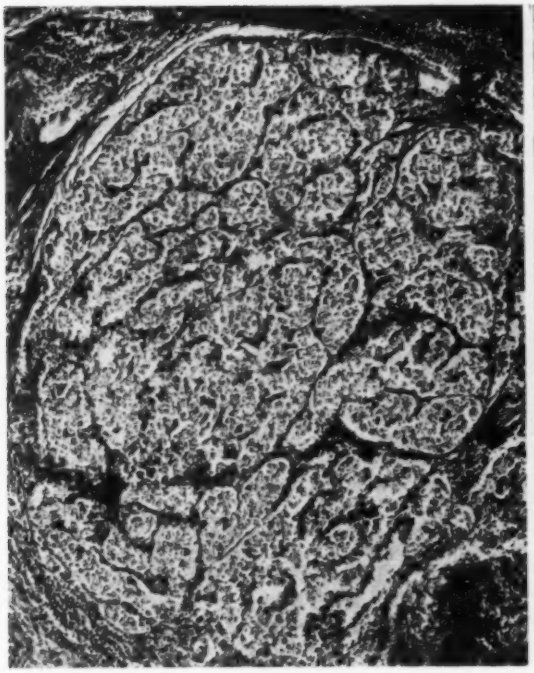

Fig. 21

Fig. 22

Fig. 23

Fig. 24

eliminated by securing equivalent results in four mounts. Functional capacity on the part of this structural type is presently considered quite exceptional.

A Hurthle cell adenocarcinoma is pictured in Figure 23. The tumor occupies the central portion of the section and is surrounded almost entirely by a rim of adjacent thyroid tissue. The tumor itself is partly hemorrhagic and broken down. The corresponding radio-autograph (Fig. 24) fails to show the deposit of any isotope in the tumor itself.

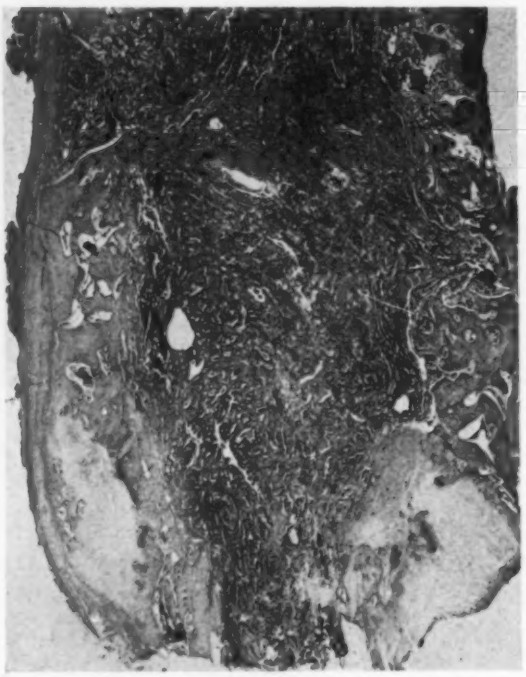

FIG. 25

FIG. 26

The uniformly good pick-up pattern of so-called benign metastasizing struma can be seen in Figures 25 and 26. In the tissue section (Fig. 25) one sees the distribution of the tumor within a portion of rib. The radio-autograph (Fig. 26) gives a very complete outline of the central tumor and its peripheral extensions into the cortical bone.

SUMMARY OF RADIO-AUTOGRAPHIC AND HISTOPATHOLOGIC FINDINGS

From the foregoing it is clear that certain types of thyroid carcinoma do possess the ability to accumulate radioactive iodine. Furthermore it appears that structural type is an important determining factor. Generally speaking, pick-up of the radioactive material is closely linked with structural qualities which include orderly cell arrangement in follicular pattern and the presence of colloid-like material. It is evident that these morphologic factors hold true for metastatic as well as for primary tumors.

In the 19 cases included in this study there were 10 in which the presence of radioactive material was detectable by means of radio-autographic determinations. Five of these were examples of benign metastasizing struma. The remaining 5 had the structure of follicular adenocarcinoma

in some portion of the material studied. It has already been pointed out that there is frequent interplay between papillary and follicular features in certain thyroid carcinomas. Due to technical difficulties it is not always possible to orient the pick-up pattern in sufficient detail to be certain that any of the papillary portions of the tumor were functional. In 2 cases the evidence of pick-up in limited papillary areas was suggestive but not absolute. In only 1 case in this series of 19 was there evidence of function in a tumor that was regarded as highly malignant and free from colloid or follicular pattern. In the 9 cases yielding negative results there were 3 Hurthle cell carcinomas and the remainder were either solid alveolar or more anaplastic thyroid carcinomas. It is necessary to state that in some of those cases which yielded positive radio-autographs there were portions of tumor that gave no evidence of ability to pick up the isotope. The only type of thyroid carcinoma not yet studied is spindle and giant cell carcinoma. It would appear optimistic to believe that this type would be functional.

The reporting of positive findings in 10 of 19 cases of thyroid carcinoma is misleading unless qualified and it is stressed that many of these 19 cases were selected. Tracer doses have been administered to a number of cases in which functionability was demonstrated to be absent by other means such as determining that excised or in situ tissues did not contain radioactive material. On the basis of present findings and the estimation of the relative frequency of the various types of thyroid carcinomas approximately 15 per cent of thyroid cancers may be expected to accumulate radioactive iodine in some degree. The most favorable histopathologic type of thyroid cancer is the so-called benign metastasizing struma. Thus far, no case of this type has yielded a negative result. Nearly the same statement can be made in regard to orderly follicular thyroid carcinoma but the avidity of the cells of this tumor does not approach that seen in metastasizing struma. Attention is again directed to the lack of uniformity in the pick-up pattern of various thyroid carcinomas that prove to be functional in some measure. This is largely explained upon the structural grounds previously discussed but it is to be remembered that very poor pick-up and sometimes no pick-up at all is seen in some portions of thyroid tumors whose structure would ordinarily indicate the ability to retain the isotope.

From the above discussion it is apparent that despite the rather close relationship between histopathological pattern and radioiodine pick-up, a clean-cut decision on the advisability of palliative or curative radioiodine therapy cannot be made on the basis of a limited biopsy since such a specimen may not reveal the more favorable histpathologic patterns that may be present. For example, in a recent case not included in this series the initial pathologic material revealed an unfavorable papillary tumor. In spite of this a tracer dose was administered and, by external measurements with the Geiger-Müller counter, evidence of appreciable uptake was found in a bulky rib metastasis. Biopsy from this area yielded tumor tissue in which the histopathologic structure was quite different from that previously seen, being orderly follicular carcinoma, a relatively favorable form for radioiodine therapy. A very conservative attitude on this subject would point to the treatment of metastasizing struma only.

The hopelessness of metastatic thyroid cancer and the radioresistance of the more functional forms, however, counsel a more extended therapeutic trial in all cases in which external measurements reveal the presence of the isotope in metastasis irrespective of the possible heterogeneous deposition of iodine that may be present therein. In this connection it must be borne in mind that radio-autographs do not indicate the exact distribution of radiation in a tumor because they are obtained from

radiation originating in a few microns of tissue and not in a tissue block of thickness comparable to the range of the beta particles.

Mention also must be made of the fact that since the isotopes of radioiodine emit gamma rays, there remains the possibility of administering the isotopes in amounts sufficient to deliver gamma radiation throughout heterogeneous tumors by using the functional foci of the latter as so many sources of interstitial radiation instead of relying exclusively on the corpuscular radiation.

The selective deposition of iodine in the organism and the lack of untoward effects in the case treated by Seidlin, Marinelli and Oshry[8] provide some justification for such an attempt, but lack of experimental data on the radioiodine tolerance of the human organism precludes closer estimate of the probability of success by such a procedure. Therapeutic attempts now in progress will provide the answer to this interesting question.

Sight must not be lost, either, of the possibility that therapeutic means may be developed to increase the deposition of radioiodine in thyroid tumors. If, for example, thyrotropic hormone could be shown to increase functional activity in these tumors a potentially useful booster mechanism would become available. Temporary kidney block should also be contemplated inasmuch as it is known that this organ, through its excretory function, competes with functional thyroid tissue for whatever inorganic iodine is present in the blood stream and may prove ultimately to be the organ which sets the upper limit of tolerance to radioiodine administration.

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DISCUSSION OF PAPERS BY DRS. JONES; LOW-BEER; COPP, AXELROD AND HAMILTON; AND MARINELLI, FOOTE, HILL AND HOCKER

DR. ROBERT S. STONE, Berkeley, Calif. It is now well over ten years since artificial radioactive materials first began to be used, and we find ourselves still asking "What is going to happen to them in the future as therapeutic agents, or what other useful purpose will they serve"? The truth of the matter is that they have served tremendously useful purposes in non-spectacular ways, but that the things which the lay press tries to make spectacular from time to time, and which we would like to be spectacular in our medical work, just haven't materialized as yet. We keep trying to find new ways in which radioactive materials will be useful.

I think we should recognize that there is not likely to be any spectacular way in which they are going to be useful and that we might as well take the step-by-step progress which has been going on and which will continue to go on as the main method of advancing. We can continue to hope that something of a more spectacular nature or a more rapid advance may develop. You all recall that the early work of Dr. John Lawrence in the treatment of leu-

kemia with radioactive phosphorus gave promise of greater things to come. Instead, just recently Dr. Lawrence himself published a paper in your journal which showed that it probably never will be possible to kill leukemic tissue without killing the bone marrow itself. Nevertheless, the treatment of leukemia with radioactive phosphorus has become a standard and very satisfactory means of treatment.

Dr. Jones mentioned many of the steps forward that have come and yet the only selective thing that has definitely been found in his work is the location of the chromium phosphate in different tissues. We look forward to a time when the biochemists and physiologists will be able to localize various radioactive compounds in selected tissues and then we may be able to apply them successfully to therapy.

Dr. Copp's paper dealing with how certain elements are metabolized in the body is one of the steps in that direction. His results do not yet suggest any way of applying his methods to therapy. It was developed, of course, to help out on the plutonium project (Manhattan Project) with regard to where plutonium was locating in the body, but it is one of those studies, of which there were a great many done during the war on the plutonium project, to let us know where the various radio elements are going to locate. It isn't an easy thing to figure out how we are going to help patients with these elements, but I think a considerable advance has been made.

Dr. Low-Beer's work has been very interesting to watch. It has been very useful work, and I think it has accomplished some things that cannot be accomplished with other methods of therapy, but after a number of years have gone by, if you have given large doses of beta rays from phosphorus, you begin to find thin papery skin and telangiectasia the same as you find after any large dose of radiation, whether it is contact therapy, or million volt therapy, and the only way to avoid affecting the skin is to treat deep tissues with some of the other materials that Dr. Jones mentioned as in the offing, or with the protons and the beta rays of high energy, which may be sent through the skin without influencing it. Then we will have the problem on our hands of getting "telangiectasia" in the deep tissues instead of in the skin, and we won't be able to detect it until it is too late.

The work from Memorial Hospital is one of the most interesting subjects. The treatment of carcinoma of the thyroid with radioactive iodine is the only example of the localization of an element being used as means of therapy. They do not bring out in the paper that the radioactive iodine for the treatment of the thyroid cost them somewhere around four thousand dollars, so it doesn't become a very economic method of treatment unless we can get some other source of iodine that will be less costly.

That brings me to one more point that I want to make in closing and that is that in order to emphasize the peaceful uses of atomic power in medicine, the Manhattan Project has taken advantage of the fact that radioactive elements are examples of atomic power. Now, of course, there are practically no radioactive elements that are the result of chain reacting piles that could not be made on the cyclotron before the war. It is just a question of quantity, and now they are coming face to face with the problem of how to distribute these elements to the country as a whole and what to charge for them.

I happen to have attended a few of the conferences recently when they were trying to work out the cost of these materials. I think that those of us who have used radioactive materials in the past will appreciate more what Professor Ernest Lawrence and his staff operating the cyclotron at Berkeley have done for us in giving us radioactive materials when we find out how much it will cost merely to pay the Army their out-of-pocket costs. These radio elements are going to be rather costly tools with which to work.

I would like to refer all of you to the recent issue of *Science** which describes how the Manhattan Project is going to distribute radio elements throughout the United States and tells considerable about what ones are available and how to obtain them. It is going to be difficult to produce and separate them. The piles, where the chain reaction goes on in controlled conditions were not built to make radioactive materials. They were built to make plutonium. It is going to require considerable expense and time to adapt the present piles and laboratories to the production of radioisotopes. This has been an interesting symposium, and the Society has profited much by the presentations.

Dr. John H. Lawrence, Berkeley, Calif. Dr. Stone has given such an excellent discussion of

* June 14, 1946, *103*, 697-705.

these papers that there really isn't much to add, and I'll speak very briefly. I think that Dr. Jones has given a very excellent discussion of the possible applications of some of these newer developments in nuclear physics to radiation therapy, and I think he has impressed upon you the numerous applications of the tracer technique in metabolic studies. He has some very exciting things he could talk about along these lines.

With reference to Dr. Marinelli and his associates' work, and also the work of Dr. Copp using the autoradiographic technique, all of us would hope that one could actually get cell definition from radio-autographic work, and some of us have tried to place our sections in a strong magnetic field so we could pull the beta rays straight out and get real cell definition. Then this technique would be very useful in this type of investigation. This work of Marinelli and Copp shows that you can't get cell definition although one can differentiate colloid from the cellular radio-iodine to some extent. The physicists tell us we are wasting our time to try to pull these beta rays straight out with any magnetic field available, so the technique cannot be improved upon by this method.

I want to add one remark regarding leukemia. In 1938 we presented exploratory work in the treatment of leukemia by radioactive phosphorus and made a progress report before this Society. We have analyzed the records of cases that have been treated since 1936. We have approximately ten years' experience, and as you all know, there is great difficulty in evaluating therapy in such a disease; you have to wait a lifetime before you get end-results in such a chronic disease.

To give you an indication of what the findings are showing in the case of the first hundred unselected cases of chronic myelogenous leukemia, the average length of life as of last week —and about 15 of these cases are still alive— and counting their length of life as of today, is about three and one-half years.

Now, in the chronic lymphatic series, analysis of a similar group of 55 cases treated since 1936 shows the average length of life to be about four and one-half years. As Dr. Stone pointed out, in this form of therapy you do not have the degree of selective irradiation you want.

In *Science* (1946, *103*, 697) there is a discussion of radioisotopes available from the pile. Between the cyclotron and the pile, these isotopes are now becoming widely available.

Vol. 58, No. 1

NEPHROCALCINOSIS*

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THE term "nephrocalcinosis" has been used to describe several conditions which have widely different etiologies. In general, they have the common finding of calcium deposits in the renal parenchyma which may be found in the pyramids alone, or in the cortex, or in both. It is the purpose of this paper to review the subject of nephrocalcinosis and to discuss the pathological and physiological processes involved. In addition, a case of chronic nephritis with extensive calcification of the kidneys, ending in typical renal insufficiency and death, is presented.

PHYSIOLOGICAL CONSIDERATIONS

The calcium, phosphorus and protein of the blood exist in intimate relationship with each other. Normally some 60 per cent of the serum calcium is in combination with protein and in this form it is non-diffusible through a colloidin membrane. The inorganic blood phosphate concentration bears an inverse relationship with the concentration of the ionized calcium, so that these ions are in equilibrium with the calcium phosphate of the blood, according to the well established chemical formula $(Ca^{++})^3 \times (P\equiv)^2 = k$, where k is a constant known as the solubility product constant. It should be noted that k is constant only for a fixed pH, having a lower value at a higher pH and a higher value at a lower pH, so that the concentration of calcium and phosphorus soluble at pH 7.4 may not be completely soluble at pH 7.5. At the normal blood pH, the relationship (Ca) × (P) = 36, where the concentrations are expressed in milligrams per cent, holds fairly well. However, this equation is dependent upon all of the blood inorganic phosphate remaining in a diffusible form, which is probably not always the case. Grollman[17] has shown that in mammals all of the inorganic blood phosphate is diffusible in the normal state, but as the calcium level is raised to levels of 12 mg. per cent or more, significant percentages of the phosphate become non-diffusible. This author postulated the formation of a colloidal complex of calcium phosphate in loose combination with protein, which would render the phosphate incapable of passage through a collodin membrane. It seems probable that such a mechanism as this was the factor which has led to some authors[13] placing the level at which metastatic calcification occurs at $(Ca) \times (P) = 100$, since such a state of supersaturation could be easily produced by the formation of the colloidal complex.

Many factors enter into control of the excretion of calcium and phosphorus. Normally over 60 per cent of ingested calcium is excreted by way of the bowel, while the greater part of phosphorus is lost in the urine. The renal threshold for calcium reabsorption is at a blood level of 7 mg. per cent,[1] so that this ion is continuously being lost in the urine, and the rate of loss is roughly proportional to the height above 7 mg. per cent at which the blood calcium lies. Renal excretion of phosphorus has been shown to be intimately related to the activity of the parathyroid gland. Parathyroid hyperactivity is associated with an intensified phosphaturia, while hypoactivity results in decreased phosphate excretion. The calcium excretion is secondarily affected in both instances. When the excretion of phosphates is rapid, the blood phosphates fall to subnormal levels, giving rise to higher calcium levels and consequent increased calcinuria. Contrariwise, when the phosphate excretion is subnormal, the blood level is increased and the blood

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calcium level falls with consequent decrease in its urinary excretion. Thus, when the excretion of phosphorus is rapid or slow as the result of parathyroid activity, the excretion of calcium is respectively also rapid or slow. In uremia, however, despite the slow excretion of phosphorus by the decreased glomerular mass, the calcium loss from the body may still be rapid as a result of the acidosis that accompanies this condition. This is due to the inability of the tubules to elaborate enough ammonia to cover the acid products of metabolism and therefore a fixed base is called upon instead. Calcium is expecially suitable because it has a double valency, allowing one ion to cover more acid, and because it has a large reservoir in the bone.

PATHOLOGICAL CALCIFICATION

Pathological calcification in human tissue may result from one of two mechanisms: (1) abnormally high concentrations of calcium or phosphate in the blocd with precipitation of calcium phosphate in healthy tissues, or (2) local tissue damage with precipitation of calcium in the presence of normal blood levels. It is significant that the areas of predilection for abnormal calcification are areas where there are marked changes in the pH of the media, or where there is an increased concentration of phosphatase. It seems most probable that this precipitation occurs from a colloidal suspension of the calcium phosphate-protein complex in instances of hypercalcemia or from non-colloidal ionic solutions when the blood levels are normal. It is not surprising that precipitation should occur more readily in the former instance, where there is already a state of supersaturation.

In the lungs one element which tends to hold calcium phosphate in solution is lost from the blood due to rapid loss of CO_2 in the change from venous to arterial blood. This is seen in the equation:

$$Ca_3(P_4)2 + 2H_2CO_3 = 2CaHPO_4 + Ca(HCO_3)2 = 3Ca^{++} + 3HPO_4^{-} + 2HCO_3^{-}$$

According to the mass-action law, the pulmonary process of removing CO_2 from the system would, by reducing the amount of H_2CO_3 present, drive the above reaction to the left and calcium phosphate would be precipitated. The gastric mucosa is a favorite site for calcification. The process of secreting acid contents into the stomach leaves the secretory cells alkaline, creating a medium in which calcium phosphate is quite insoluble. A similar process takes place in the renal tubules where acidification of the urine necessarily renders these cells alkaline. In addition, these cells are high in phosphatase. Similarly the media of the aorta and larger arteries, a favorite site for calcium deposits, are high in phosphatase.

Calcification Due to Abnormally High Concentration of Calcium or Phosphorus in the Blood. The first type of calcification occurs occasionally in hyperparathyroidism, with multiple deposits in the kidneys as well as throughout the body, particularly in the periarticular areas, the lungs, the gastric mucosa, and the large blood vessels. Similar incidences of this type of reaction have occurred following intoxication with vitamin D where blood calcium levels have reached very high levels.

In 1934, in a review of 83 cases of hyperparathyroidism, Albright, Baird, Cope and Bloomberg[2] noted that some 50 per cent of their cases had associated renal complications. Somewhat over half of these had precipitation of calcium in the renal pelves with concurrent pyelonephritis. The rest were characterized by precipitation in the tubules with resultant sclerosis, contraction, and insufficiency in renal function. They felt that the renal lesion of hyperparathyroidism was an index of the severity of the disease, while the amount of osteitis fibrosa cystica was an index of the duration of the disease. That abnormal precipitation of calcium in the kidneys can actually occur from overdosage with the parathyroid hormone was shown experimentally in the rat by Chown, Lee, Teal and Currie[12] and this can result in either acute or chronic renal failure. In the experimental animal, a

state of acute renal failure, followed very shortly by death, can be produced by massive doses of the parathyroid hormone. Albright *et al.*[2] bring this out in their review of the subject and they state that, although there had been no cases of this in man reported in the literature, they had observed a case which resembled it closely at the Massachusetts General Hospital. Recently, Rogers[29] reported 2 patients with peptic ulcers and unsuspected hyperparathyroidism in whom death from acute renal failure had occurred after a period of moderately severe alkalosis, produced by vigorous ulcer regimens. Here it would seem that the combination of the alkalosis with the pre-existing hyperparathyroidism came very close again to reproducing the picture which Albright describes in the experimental animal.

On the other hand, progression of the renal lesion into chronic renal failure has repeatedly been seen. Mayer[25] reported a case where after removal of the parathyroid tumor in a patient, who had already developed renal calcification, hypertension developed which was terminated by a dissecting aneurysm of the aorta. Johnson[20] described a case where renal insufficiency progressed to such a degree that the three parathyroids that were not involved in the primary adenoma showed the typical changes of secondary hyperparathyroidism.

The differential diagnosis between primary and secondary hyperparathyroidism in a patient with renal insufficiency is often difficult. Shelling and Remsen[32] emphasize the location of the metastatic calcification and state that in general calcification of the kidney represents primary hyperparathyroidism, whereas calcification elsewhere, and sparing the kidney, is suggestive of primary renal disease. However, diffuse renal calcification may occur in renal disease alone and in the absence of parathyroid disease. Albright *et al.*[2] lay more stress on the serum calcium level in distinguishing between the two conditions. Since primary hyperparathyroidism begins with a markedly elevated serum calcium, while that of renal insufficiency is slightly subnormal, a case with a high calcium should be considered primary parathyroid disease, while that with a low calcium should be regarded as primary renal disease. Castleman and Mallory[11] have described definite histopathological differences between primary and secondary parathyroid hyperplasias, the former being a hyperplasia of a water-clear type of cell and the latter being made up almost entirely of normal size chief cells.

The roentgen picture of the calcified kidneys in hyperparathyroidism is of little help in determining etiology, for the locus of the calcium deposits is apparently not constant. Ettinger and Magendantz[14] present a case in which the kidneys showed "innumerable areas of increased density each about the size of a millet seed lying in wedge-shaped forms conforming to the outlines of the renal pyramids." On the other hand, Brindle and Herrman[9] reported a case where the kidneys were quite diffusely outlined by calcification.

Butler, Wilson and Farber[10] in 1936 called attention to another apparently quite distinct clinical syndrome, associated with calcification of the tubules. They observed 4 infants in whom there was persistent dehydration in the absence of excessive diarrhea or vomiting and in whom there was adequate intake of food and fluid. There was a persistent hyperpnea associated with an increased serum chloride and decreased CO_2. They also reported the case of a ten year old boy who had similar chemical findings—calcium deposits in the kidney by roentgen examination and a low phosphorus rickets. Albright, Consolazio, Coombs, Hirsh, Sulkowitch and Talbott[3] did extensive metabolic studies on a thirteen year old girl with the same clinical picture.

Neither renal calcification nor rickets is an essential part of the disease. Boyd and Stearns[8] report a case of chronic acidosis and rickets in a patient where the disease process was almost certainly primarily a tubular inability to make an acid urine, but

in whom no renal calcification could be demonstrated. This is good evidence for the impression that renal calcification is secondary in nature, the type of metastatic calcification occurring as a result of local tissue damage. In Butler, Wilson and Farber's infant cases there was no involvement of the bone, attributed by Albright *et al.* to the fact that those cases represented severe and fulminating examples of the disease, in which death occurred before the bone lesions could make their appearance. Baines, Barclay and Cooke[7] recently observed a twenty-nine year old woman who had the typical metabolic findings found in the group of patients but in whom there were again no skeletal changes. Here age was probably the determining factor. These authors emphasize further that it is not essential to postulate the parathyroid mechanism to explain the low serum phosphate concentration, for the chronic acidosis is in itself enough to produce a hyperphosphaturia, which may bring about a lowered serum phosphorus. Haldane has shown that acidosis produced by ammonium chloride will increase phosphorus excretion, and be believes that this hyperphosphaturia is concerned with the buffer action of the urinary phosphates, allowing the kidneys to excrete more acid with less base. Provision of extra base in the diet, in the form of sodium citrate, would offer enough fixed base to the tubular urine so that adequate absorption of phosphates by the tubule could be accomplished. Albright *et al.* conceived of the reversal in serum phosphorus, after correction of the acidosis by the citrate, as being the result of decreased demand for calcium as fixed base, with consequent rise in the serum calcium level which removes the stimulus to parathyroid hyperactivity with subsequently less phosphaturia. It seems logical to believe that both mechanisms are at play.

Calcification in the Presence of Normal Blood Calcium and Phosphate Levels. The second type of calcification is found in those diseases of the kidneys in which the renal tissue is necrotic, severely damaged or chronically inflamed. The name "dystrophic calcification" has been applied to this type of calcification. As mentioned above, the primary factor leading to the deposition of the calcium is probably elevation of the pH due to the decrease in CO_2 production in the devitalized renal tissue. The tuberculous tubule is the example *par excellence* of calcium deposition in areas of necrosis. Calcium is occasionally deposited in tumors and cysts of the kidneys, particularly those in which necrosis and hemorrhage are present. Mercury poisoning with its extensive tubular damage is commonly followed by deposition of calcium in and around damaged renal tubules. More recently calcium has been demonstrated in casts in the renal tubules in certain cases of anuria due to sulfadiazine.

There have been several reported instances of extensive calcification of the kidneys in chronic pyelonephritis. Albright, Dienes and Sulkowitch[4] reported 2 cases in 1938 in which the infecting organism was *H. influenzae.* The blood calcium, phosphorus and proteins were normal, phenolsulfonphthalein excretion was good, but urinary concentration was only 1.008. On the roentgenogram the calcium deposits were in the pyramids. The patient's history revealed repeated passage of gravel in her urine. This is not a usual symptom in nephrocalcinosis, but may occur when calcium is deposited at the tips of the pyramids where it serves as a nidus for renal calculus formation.[6,28,30] Renal calcification involving the cortex only cannot lead to calculus formation. Wohl[35] reported renal calcification involving chiefly the pyramids in an eleven year old boy whose only symptoms were polydipsia and two times nocturia. He gave a past history of a urethral discharge. Ewell[15] and Grossman and Allyn[18] record 2 further instances of infection leading to calcification, in cases of lower urinary tract obstruction with secondary infection.

Nazari[26] first noted the occurrence of calcification in and around the tubules following prolonged and severe upper gastro-

intestinal obstruction with vomiting. Martz[24] dwelt extensively upon the pathogenesis of these changes and stated that they were due to the marked alkalosis present. According to this concept calcium precipitation results from the continued excretion of acid urine in spite of a systemic alkalosis. With prolonged vomiting, there is a loss not only of chloride, but also of significant quantities of sodium from the stomach. If the sodium loss is great, the blood sodium level may begin to fall. When this occurs, the kidneys attempt to conserve the diminishing supply of the body's base. In order to do this, they must secrete an acid urine, in the face of the alkalosis, instead of the previously alkaline urine elaborated. That the kidneys should not preferentially conserve sodium, whereas the body is even more depleted of chloride, is probably best attributed to the fact that the loss in acid radicles represented by the chloride can be somewhat compensated for by an increase in the bicarbonate content of the blood, while there is no suitable ion to compensate for the sodium loss. Martz feels that strong evidence in favor of this series of electrolytic events is the fact that, when these individuals are given only saline as parenteral fluid therapy, their urines become alkaline again, while the administration of acid salts such as ammonium chloride or calcium chloride only makes them worse. The saline replenishes the sodium needed, whereas the acid salts do not. In any case, the process renders the tubular cell even more alkaline than that afforded it by the alkaline blood serum. A medium is thus produced in which the solubility product constant of calcium phosphate is easily exceeded and precipitation necessarily follows. That this elaborate mechanism is at least not always necessary is brought out by the series of patients studied by Kirsner, Palmer and Humphreys.[21] Their patients were given massive alkali therapy to the point of alkalosis and autopsy findings revealed marked calcium deposition in the collecting tubules. Here the urine had no reason to turn acid, since there was always excessive base, due to the nature of the production of the alkalosis. In this case the cause of the precipitation must be, to a large extent, based upon concentation of the solutes in the lumina of the distal portion of the tubule, plus the continued alkalosis of the urine in this segment. Both factors tend to precipitate calcium phosphate. Here one would expect to find the calcification within the lumen of the tubule, at least in the very early phase of the lesion, whereas in the case mentioned by Martz, one would expect that the first precipitation would occur within the cell itself. The difficulty of demonstrating this differential point microscopically is in finding an area where the lesion is an early one in which the structure of the surrounding tissues has not been destroyed, for such damage would probably produce further deposition of calcium, which would obscure the original focus.

That these cases of calcification from alkalosis produced by vomiting do not show metastatic calcification elsewhere in the body is also considered by Martz. He suggests that in the lung, where release of CO_2 into the alveoli is a factor in allowing calcium phosphate to precipitate, this factor is no longer at play. In an extreme state of alkalosis the CO_2 is retained through the medium of shallow and slow respirations, in order to conserve bicarbonate to replace lost chloride and cover excessive base. In the stomach, after prolonged vomiting, there is cessation of the production of hydrochloric acid by the gastric mucosa (as shown by Gamble[16]), so that eventually the stomach contents may even become alkaline. Here then the cells are no longer left alkaline by their secretory process and so precipitation of calcium does not occur.

Calcium deposition in renal tissue was produced in rats by Thorn, Clinton, Farber and Edmonds[33] following repeated short exposures to reduced atmospheric pressure. Calcium was deposited between collecting tubules at the corticomedullary junction. It was postulated that these deposits resulted from alkalosis accompanying the

blowing off of carbon dioxide due to hyperventilation stimulated by the anoxia resulting from reduced atmospheric pressure. These authors point out that similar lesions are found in the kidneys of children manifesting hyperpnea from various causes.[10]

CASE REPORT

The patient, W. W. (P.B.B.H. No. 10352) a male, aged twenty-six, laborer, was sent to the Peter Bent Brigham Hospital in July, 1943, by Dr. Albert Johnson of Keene, New Hampshire, for an evaluation of his renal status. Dr. Johnson had found, by roentgen examination, extensive calcification of both kidneys. The patient suffered from otitis media of the left ear at the age of ten, but otherwise had enjoyed excellent health until September, 1937. At that time he developed a severe sore throat with chills and high fever. However, he was able to continue doing hard manual labor for one week, when he rested for three days and returned to full time work. Six weeks later dysuria and edema of the face, ankles and legs developed. No gross hematuria was noted. He was placed on a diet of skim milk with no meat or added salt and put to bed for four weeks. Under this regimen, the edema disappeared and he was able to return to work. Shortly thereafter, a tonsillectomy was done because of frequent upper respiratory infections, but the patient continued to have attacks of sore throat. During this time, ankle edema was frequently noted, particularly after a hard day's work. Also, he tired easily, tended to be short of breath, and when tired would occasionally have twitching of muscles and severe muscle cramps. His physician told him that he had hypertension and constant albuminuria and cylindruria. The patient was placed on a diet of 1 to 2 quarts of skim milk daily and of low salt and protein content. During the four months following his initial illness the patient's weight dropped from 191 to 164 pounds, and during the next six years only 3 pounds were regained.

The physical examination at the time of his first admission showed the patient to be a muscular, tall young man in no distress. The temperature was 98.8° F., respirations 20, pulse 80, and blood pressure 196/120. There was no peripheral edema. Examination of the eyegrounds showed slight narrowing of the retinal arterioles. The mucosa of the throat was red and injected. The lungs were negative to auscultation and percussion. The heart was not enlarged. Rhythm was regular. A Grade 1 systolic murmur was heard over the apex. The aortic second sound was greater than the pulmonic second sound and was of tambour quality. The kidneys were said to be palpable. Reflexes were hyperactive. The remainder of the physical examination revealed nothing of note.

Laboratory Data. The blood Hinton test was negative. Examination of the urine showed a persistent++++protein, no sugar and from 0 to few red blood cells and white blood cells per high power field of the sediment in centrifuged specimens. Granular casts were seen in the sediment on one occasion. The hemoglobin was 14.3 grams, red blood cell count was 4,750,000 and white blood cell count was 8,200. The differential count gave 65 per cent polymorphonuclear leukocytes. The blood urea nitrogen was 30, the non-protein nitrogen 45, and the total proteins 4.3. The albumin was 1.6 and globulin 2.7. The fasting blood sugar was 91 mg. per cent. CO_2 was 22.9 mM/l, blood chlorides 108 mE/l, blood phosphorus 1.5 mM/l, blood calcium 4.6 mEq/l and the alkaline phosphatase was 1.1 Bodansky units. The stool was negative for occult blood. Cultures of the urine were sterile on two occasions, while *Staphylococcus albus* was cultured from one specimen and diphtheroids from another. The phenolsulfonphthalein test showed 10 per cent excretion in fifteen minutes, 40 per cent in two hours with a total volume of 720 cc. The Sulkowitz test was +. The specific gravity of the urine was 1.015 in the overnight concentration test. The blood circulation time, using decholin, was sixteen seconds. Six grams of protein per liter were found in the urine.

The patient was cystoscoped and urine collected which contained no red or white blood cells or casts. Dye injected intravenously appeared in the urine in four minutes, but less than 1 per cent of the dye was excreted in 10 minutes. The electrocardiogram was normal.

Roentgen examination confirmed Dr. Johnson's finding of extensive and uniform finely granular calcification of both kidneys (Fig. 1). No calculi could be identified in the kidneys, ureters or bladder. Retrograde pyelograms revealed normal renal pelves and calices distinctly visible through the overlying calcification. The kidneys measured:—right 14.0 by 6.5 cm., left 14.0 by 6.2 cm. on the roentgenograms. The bones of the pelvis, spine, chest and skull showed the normal bone detail and calcium

content of a young man, with no osteoporosis or cyst formation. There was no cardiac enlargement, in fact the heart was 15 per cent below the predicted average according to Ungerleider's height-weight chart.[34] The lungs were clear (Fig. 2). The skull and sella turcica were normal. There was marked calcification of the larger pelvic arteries at this time.

Hospital Course. Fluids were forced to 3,000 cc. daily and the patient given 100–125 gm. of protein each day. Calcium intake was limited to 0.5 gm. per day.

He was discharged on the twentieth hospital day with no change in his renal status.

The patient returned to the hospital in January, 1945, one and one-half years later, because of itching of the skin of eight weeks' duration. Following his first discharge he had felt well until the onset of the itching. However, one year before the second admission he had an attack of left otitis media with perforation. The patient continued to have peripheral edema but at no time noticed hematuria or headaches. Ten weeks before entering the hospital the patient suffered from frequent nausea and vomiting and because of these symptoms the fluid intake and food ingestion was low. At the time the skin began to itch, a rash, made up of small papular or pustular lesions, appeared. These lesions would break open and be followed by scabbing and scar formation.

Fig. 1. Plain roentgenogram of the kidneys, July 7, 1943, showing marked calcification of both kidneys particularly in the cortices. Kidney measurements given in text.

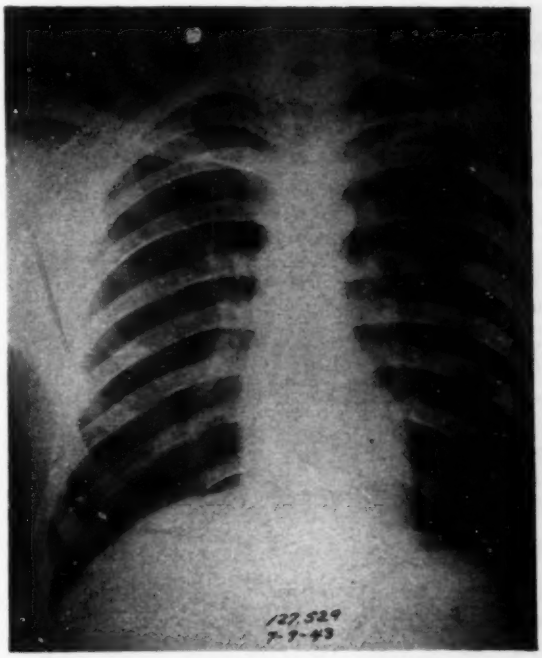

Fig. 2. Seven foot roentgenogram of the heart, July 7, 1943. Patient's measurements were: height 6 feet 1 inch; weight 167 pounds; predicted transverse diameter 128 mm.; measured transverse diameter 109 mm.

At the time of the second admission the temperature was 98.4° F., pulse 90, respirations 24 and blood pressure 200/120. The skin was dry and "sallow." There were numerous papules over the body, many of which were scarred and surrounded by areas of pigmentation. Examination of the fundi showed some narrowing of the arterioles but no exudate or hemorrhages. The left ear drum was perforated and a small amount of exudate was present. The heart was slightly enlarged to percussion and a Grade II systolic murmur was heard over the precordium. The lungs were clear to auscultation and percussion. Examination of the abdomen was negative. Edema was demonstrated over the sacrum and left ankle.

Laboratory Data. The urine was pale yellow and cloudy. The pH ranged between 5.5 and 6.0. The specific gravity varied between 1.010 and 1.012. There was ++++ albuminuria. Red blood cells averaged 20 to 30 an d white

blood cells 6 to 10 per high power field. There were many granular and fatty casts. The hematocrit was 22 and fell to 18 terminally, repeated white blood cell counts were in the 6,000 to 8,000 range and the differentiated counts were normal. The blood sedimentation rate was 2.4 mm/min. At the time of admission the blood urea nitrogen was 177 mg. per cent,

FIG. 3. Plain roentgenogram of the kidneys, April 7, 1945. Note decrease in size of the kidneys. Right kidney is depressed by the enlarged liver and rotated on the horizontal axis. Kidney measurements given in text.

non-protein nitrogen 229 mg. per cent, total protein 7.2 gm. per cent, CO_2 17.8 mM/l and chlorides 96 mEq/l. Blood phosphatase was 0.8 Bodansky units, blood calcium 4.3 and blood phosphorus 5.6 mEq/l. The circulation time was 15 sec., the vital capactiy 2,500 cc., basal metabolic rate −5 per cent. Ketosteroids excretion was 4.3 mg. in twenty-four hours. The standard urea clearance test showed 6 per cent excretion in one hour. The electrocardiograms showed T1, T2 and T3 to be flat with a normal lead IV.

Re-examination by roentgen ray revealed the uniform finely granular calcification of both kidneys, apparently the same in type and degree as at first examination, but the kidneys had decreased in size, now measuring: right 10.5 by 5.5 cm., left 12.0 by 5.3 cm.* The roentgenograms were taken with the same technique used eighteen months earlier (Fig. 3). The heart had increased in size, now measuring 4 per cent above the predicted average for the patient's height and weight. All of the visualized bones again were of normal texture and appearance, with normal calcium content for a man of his age. No calculi could be identified. The lungs were clear. Later roentgen examinations revealed progressive terminal enlargement of the heart, pulmonary congestion and hydrothorax and a probable pericardial effusion.

Hospital Course. The patient was placed on a moderate salt, high caloric, 80 gram protein alkaline-ash diet. Therapy consisted of four blood transfusions, parenteral hypertonic saline and glucose, forced fluids, vitamins, iron and creamalin. The itching of the skin persisted and one of the pustular lesions was removed for study. Microscopic sections showed scarring and lymphocytic infiltration of the subcutaneous tissue with calcium deposition. Following therapy the edema increased and the patient was digitalized in an effort to improve his circulatory status. Southey tubes were used with some initial success but with eventual failure in relieving the edema. Four weeks before death a pericardial friction rub developed which persisted until death. The blood urea nitrogen fell to 72 mg. per cent in the first few days and gradually rose to 135 mg. per cent, the CO_2 rose to 25.6 mEq/l and then fell to 16. Chlorides gradually dropped to 76 mEq/l. The patient developed acidosis, air hunger, became disoriented and died on the 108th hospital day with cessation of respiration followed by stopping of the heart.

Autopsy Findings (P.B.B.H. No. A-45-77). The body was that of a normally developed and nourished white male. The appearance was that of a sthenic, muscular individual who appeared older than the stated age of twenty-eight. The skin was dry and green-brown in color. Papular lesions were present over the face, neck and chest and to a lesser degree the back, abdomen and extremities. The lesions were firm, slightly raised, with grey edges and brown centers which were frequently encrusted or ulcerated. They measured approximately 5 mm. in diameter. Histopathological examination of one of these

* The right kidney measurements are not reliable as the kidney was depressed by the enlarged liver. At autopsy five weeks later, the kidneys measured: right 11.0 by 5.9 cm., left 10.5 by 5.4 cm.

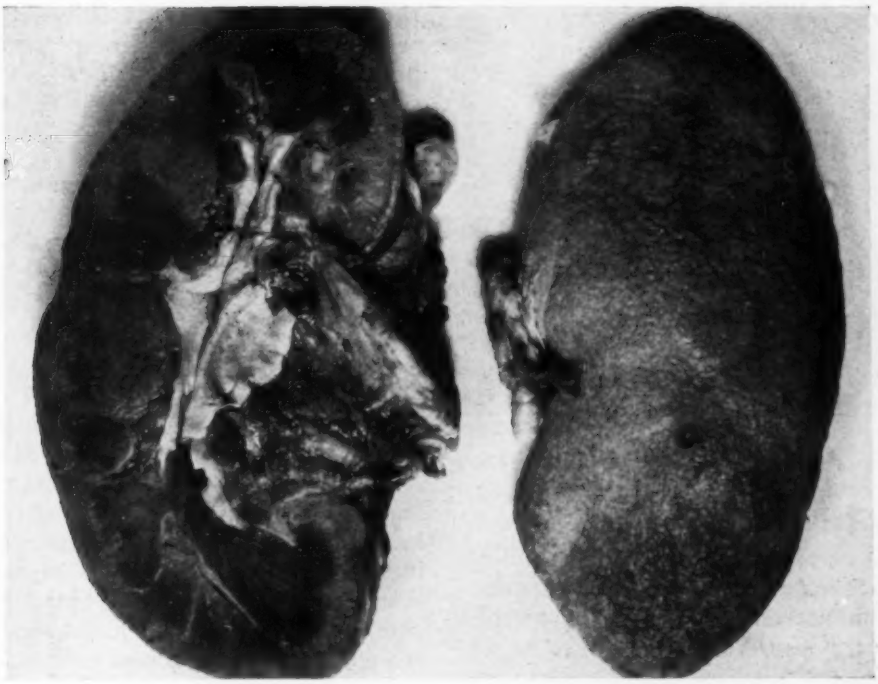

Fig. 4. Gross appearance of the kidneys at autopsy. The small white calcified nodules can best be seen scattered throughout the cut surface of the cortex.

lesions showed moderate hyperkeratosis of the epidermis which was lightly infiltrated by polymorphonuclear cells. The epidermis extended downward into the cutis and several segments were detached and surrounded by dense fibrous tissue which was sparsely infiltrated by lymphocytes. Keratinization with pearl formation was noted in some of the epidermoid projections and calcium was found in one of the pearls. There was marked pitting edema extending from the feet upward to the thighs.

The parietal and visceral surfaces of the pericardium were covered by a grey, shaggy fibrinous exudate. The heart weighed 790 grams. The left and right ventricles were markedly enlarged and their walls measured 2.4 cm. and 0.5 cm. in thickness respectively. No valvular or myocardial lesions were found and there was no evidence of calcium deposition. The right lung weighed 800 grams and the left lung 700 grams. Considerable frothy, clear, blood-tinged fluid could be expressed from the cut surfaces and microscopic examination demonstrated marked pulmonary congestion and edema. No calcium was found. There was 400 cc. of clear thin amber-colored fluid in the right thorax.

The liver weighed 2,700 grams and the gross and histopathological findings were those of marked chronic passive congestion.

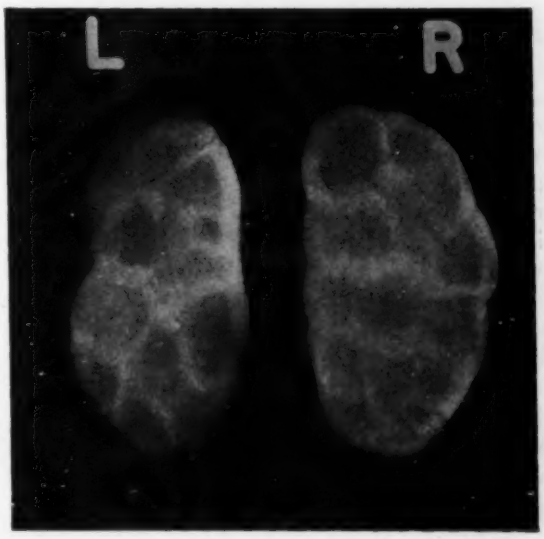

Fig. 5. Roentgenogram of excised kidneys after autopsy. Note the fine granular calcification, most marked in the cortices faintly outlining the kidney lobules.

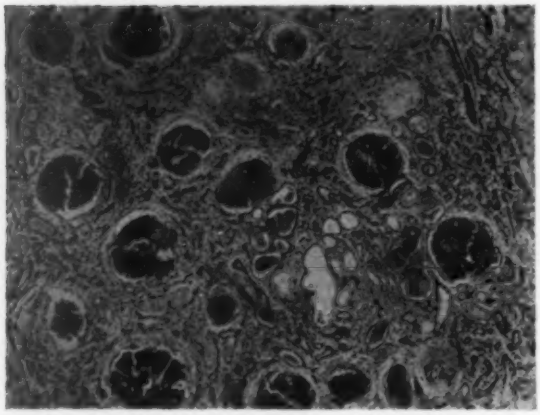

Fig. 6. Low power photomicrograph showing the nature of the renal damage.

The right kidney weighed 160 grams and the left weighed 180 grams. The kidneys were similar in appearance and are described together. The renal capsules were slightly thickened and stripped with difficulty, exposing a uniform and finely granular, pale brown surface. Cut sections showed the cortex to be well demarcated from the medulla and to measure from 6–7 mm. in width. The most striking finding was diffuse finely nodular calcification throughout the cortex, which imparted to the cortex a sandpaper-like quality as the examining finger was rubbed across the kidney. When the kidneys were cut, a gritty sensation was observed. Innumerable small calcified granules measuring from 1 to 2 mm. in diameter were found throughout the cortex (Fig. 4 and 5). These could be scraped free of the cut surfaces leaving small smooth-walled pits. These granules were grey-white and semitranslucent. The medulla was free from calcification. The tubular striations could be identified and the papillae were pointed. There was moderate thickening of the walls of the pelvic vessels. The calices, pelves and ureters were not remarkable and were free from calcification and calculi (Fig. 4).

Representative blocks of kidneys were fixed in Zenker's acid solution and 10 per cent formalin. Sections were stained with eosin-methylene blue, hematoxylin eosin, Mallory's phosphotungstic acid, Mallory's aniline blue, and Kossa's silver stains. The glomeruli were severely damaged. Large numbers were completely hyalinized. The basement membranes of many other glomeruli were thickened by hyalinized connective tissue and these glomeruli appeared atrophic and bloodless (Fig. 6). Still other glomerular tufts were prominent due to increase in cellularity and a few polymorphonuclear leukocytes were present in the involved tufts. The capsular epithelium was often cuboidal or proliferating and "crescent" formation was common.

The most striking histopathological finding was the presence of completely or partially calcified bodies throughout both the convoluted and collecting tubules of the cortex (Fig. 7). These bodies gave a positive reaction for calcium when stained with Kossa's silver stain. These were roughly the shape of the dilated tubules in which they were found. Those casts that were incompletely calcified were pale, amorphous and acidophilic. Occasionally remnants of flattened tubular cells were found lining the tubules containing the casts but in most instances the lining epithelium was absent. Rarely calcified bodies were found beneath the tubular epithelium but here the arrangement of the epithelium was such as to suggest that the epithelium had regenerated over the calcified material.

No calcified bodies were noted in the pyramidal tubules. The cortical tubules without casts were dilated and lined by flattened epithelium. Occasionally polymorphonuclear leukocytes, red blood cells and precipitated protein were present in the pyramidal tubules. There was a moderate increase in interstitial tissue with definite increase in fibrous tissue. This was particularly marked about fibrosed glomeruli. Here, too, was diffuse lymphocytic infiltration.

There was definite hyaline thickening of the

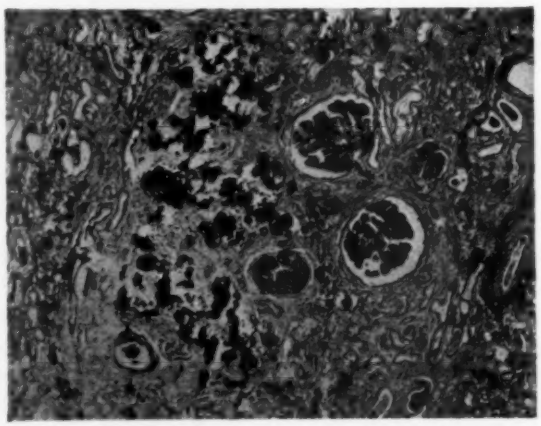

Fig. 7. Kossa's silver stain for calcium illustrating the marked calcium deposition in the cortical tubules.

walls of the arterioles and intimal and medial proliferation and thickening of the small and medium-sized arteries. In addition, occasional arterioles were found in which there was definite hyperplastic proliferation of the intima.

The parathyroid glands were homogeneous and light pink-brown in color. Section showed marked increase in cellularity with almost total disappearance of fat tissue. Chief cells were by far the most abundant. These cells were polygonal with pale cytoplasm and the nuclei were round and regular. No adenomas were found.

The adrenal and thyroid glands were not remarkable.

There were no gross alterations in the skeletal system, nor was any change noted in the bony pattern of the vertebral and femoral marrow. There was no calcification of any of the blood vessels examined.

Permission for examination of the brain was denied and the pituitary gland was not examined.

Anatomical Diagnoses: Chronic glomerulonephritis, severe; calcinosis of skin and kidneys; parathyroid hyperplasia, secondary; fibrinous pericarditis; hypertensive heart disease; pulmonary congestion and edema; hydrothorax, right; chronic passive congestion of viscera.

DISCUSSION

So far as could be ascertained in reviewing the literature, this case is unique. To summarize, the problem was that of a patient who, six years prior to first being seen in this hospital, suffered from a streptococcal throat followed by what appears to have been a typical acute glomerulonephritis. During the acute stage of his renal disease the patient was placed on a high milk diet, which was maintained for the following six years, during which time he continued hard manual labor. At the end of this time, because of the gradual onset of symptoms of renal insufficiency, a roentgenogram was taken of his kidneys and the extraordinarily extensive calcification was found. The next two years, the period during which he was observed in this hospital, were characterized by progressive decline with the development of terminal uremia, a course similar to that commonly seen in chronic glomerulonephritis. So far as could be determined, the presence of the calcium in the kidney was no more than a contributing factor in the production of the renal insufficiency. The striking calcification of the kidneys revealed by roentgen examination could easily be differentiated from that usually seen in hyperparathyroidism where actual calculi are found in the renal pelves and calices, but not from the metastatic calcification which could be the result of an unusual degree of hyperparathyroid activity as described by Albright *et al.*[2] The normal bone detail, however, was considered to be evidence against this hypothesis. Calcification due to tuberculosis also appears quite different, having an amorphous appearance, usually grossly lobulated and as a rule limited to one side when as extensive as in this case. Calcification in renal tumors, vascular anomalies, infarcts, etc., could be ruled out by the uniformity and symmetry of the calcium deposits. In fact, the appearance by roentgen ray was unique in our experience, and could be attributed only to some disease or injury uniformly involving all of the renal tissue.

The fact that the heart measurements were below normal at first and only 4 per cent above average four months before death, when at autopsy the heart weighed 790 grams, was disturbing to say the least, and proves again that heart measurements falling within the normal range may not exclude a considerable degree of cardiac hypertrophy. Of course, it is also true that the weight of a heart at autopsy is not a reliable index of the size of that heart during life, if dilatation has been present, but that was not the problem in this case.

There was no evidence that would put this case into any of the groups characterized by extensive renal calcification, which were discussed earlier. Positive evidence against hyperparathyroidism was the normal blood calcium and phosphorus levels which were present when first seen. It is to be emphasized that at this time the renal calcification was already as extensive as it was ever to become. Repeated cultures of

the urine revealed either nonspecific contaminants or were sterile, and the urinalyses, symptomatology, course and autopsy findings lent further evidence to the fact that renal infection played no part in the pathogenesis of the calcification. The specific dysfunction of the tubules associated with calcification, as described by Albright, Consolazio, Coombs, Hirsh, Sulkowitch and Talbott, is likewise ruled out by lack of the specific blood chemical changes that characterize this syndrome.

It is suggested that the following series of events were productive of the renal changes observed. Early in the disease, when there was still active inflammation in the renal parenchyma, the patient consumed enormous quantities of milk, so that necessarily large amounts of calcium were excreted in the urine. Under normal circumstances a calcium intake of this degree can be responsible for such high concentrations of calcium in the urine that precipitation may occur and renal stones be formed. In this instance there was at the time of hypercalcinuria active degeneration of renal tissue creating a medium in which precipitation would be likely to take place. That the distal convoluted and collecting tubules should be the site of this precipitation is to be expected, as it is in these areas that the urine is finally concentrated to the point where the calcium concentration might be expected to be at or above the level of saturation. It should be noted that we feel that there were two separate and distinct processes at work, the one being the result of the other. The first was the occurrence of an acute nephritis, which subsided into a subacute or latent phase, and which eventually was responsible for such scarring that a state of renal insufficiency resulted. The second was the laying down of calcium in the damaged renal tissue. This probably was the work of years of high urinary concentrations of calcium, with concomitant smouldering renal activity providing the tissue damage. The added insult of the calcium deposition in the kidneys may have contributed to the renal failure, but it was certainly not the prime factor.

Because the vague reports of early alkali therapy could not be substantiated in a review of this patient's case history, this explanation of the pathogenesis of the renal calcification has been given only passing mention. However, if such were actually the case and this man did receive large amounts of alkali at the time that he suffered his original acute renal damage, or shortly thereafter, then the elevated urinary pH would tend to precipitate the calcium in the renal parenchyma.

SUMMARY

1. The subject of nephrocalcinosis is reviewed and the pathological and physiological processes are discussed.

2. A case of glomerulonephritis with extensive calcium deposition is presented and the contributing physiological phenomena are considered.

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THE SIGNIFICANCE OF INDENTURES IN THE OUTLINES OF THE ATRIA OF THE LATERAL VENTRICLES AFTER AIR FILLING

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AFTER encephalography or ventriculography there may be visualized one or two indentures unilaterally or bilaterally in the atrial regions (the junction of the body with the temporal and occipital horns) of the lateral ventricles. The first or more rostral indenture or defect is known as the glomus indenture and the second in the caudal margin of the atrium of the ventricle is known as the calcar avis indenture.

It is the purpose of this paper to explain the significance of these identures and to differentiate the normal from the pathological.

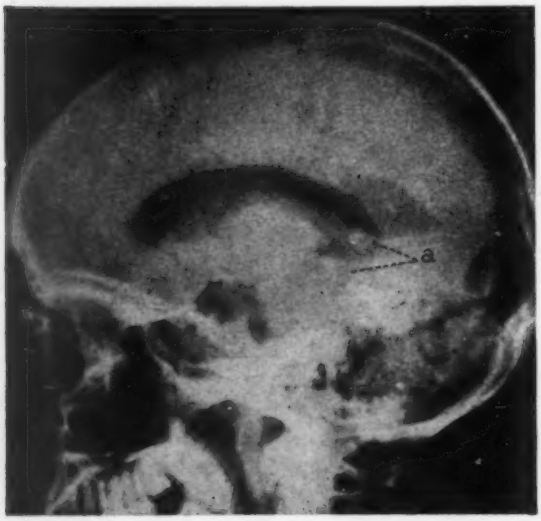
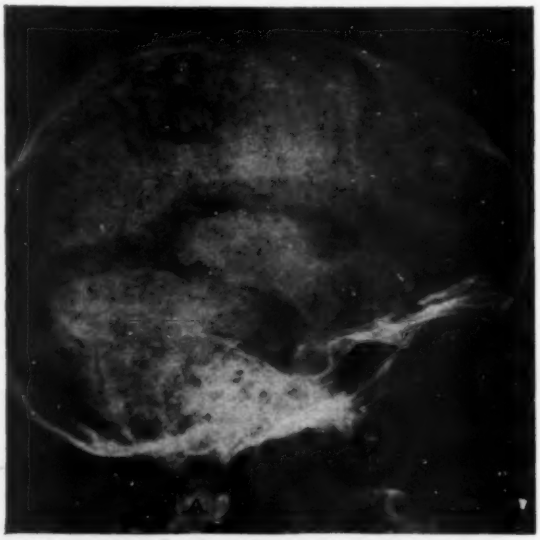


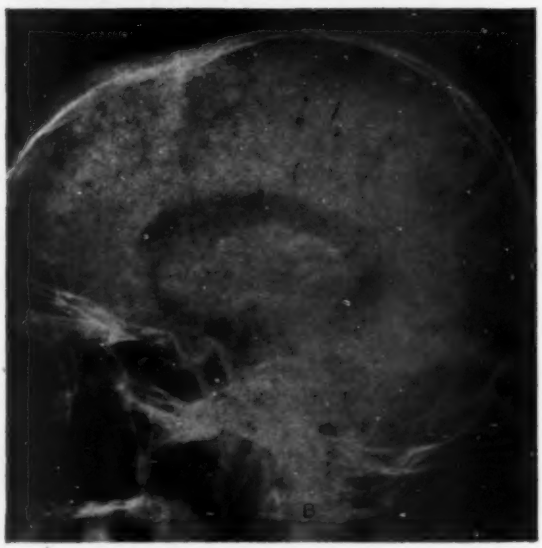
FIG. 1. Two calcified portions of the choroid plexus are seen at *a*. (From Pancoast, Pendergrass, and Schaeffer. The Head and Neck in Roentgen Diagnosis.)[5]

FIG. 2. Demonstrating asymmetry of the posterior horns on the same patient. *A*, large posterior horn on one side and *B*, a very small posterior horn on the contralateral side.

1. GLOMUS INDENTURE

The first indenture or defect occurs in the lower wall, just rostral to the subdivision of the lateral ventricular body into an occipital and a temporal horn (atrial





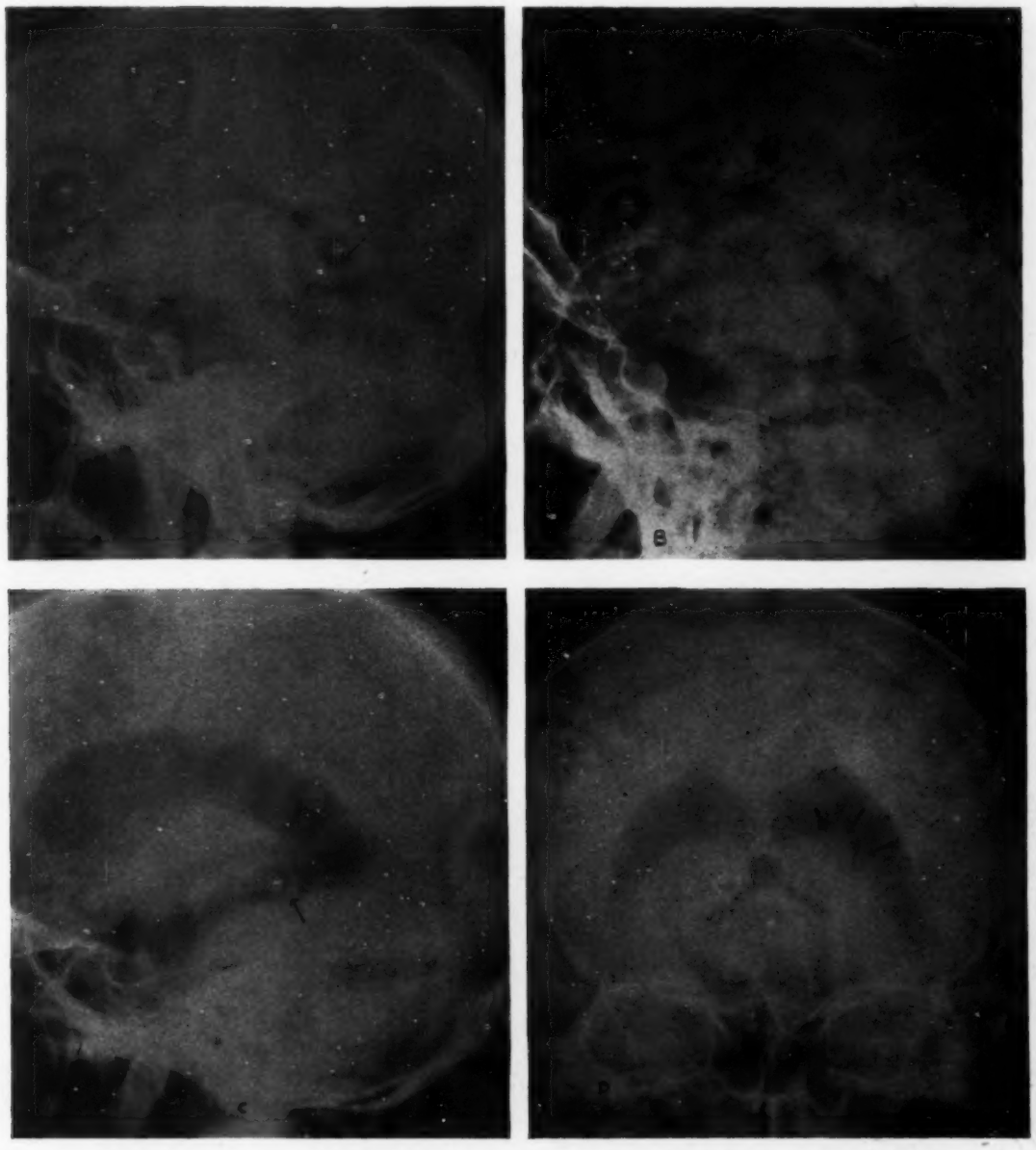


Fig. 3. *A*, small glomus defect. *B*, moderate sized glomus defect. *C*, large normal sized glomus defect. *D*, same case as *C* in the sagittal view.

region), and is known as a glomus indenture. It is produced by the upward and backward projection of the choroid plexus as it makes a sharp turn from its position in the floor of the lateral ventricle (between the basal ganglia and the thalami) and follows the ventricle around the pulvinar into the inferior horn. The portion of the plexus where the bend occurs forms a globular mass which is called the glomus. Here the plexus tissue is more abundant and is the region where calcifications may occur. Dyke found an incidence of glomus calcifications in 5.1 per cent of individuals.

For measurement purposes the lateral views are utilized. The glomus shadow, however, may also be seen in the sagittal views in the lower and medial aspect of the atrium.

When the glomus shadow itself is small

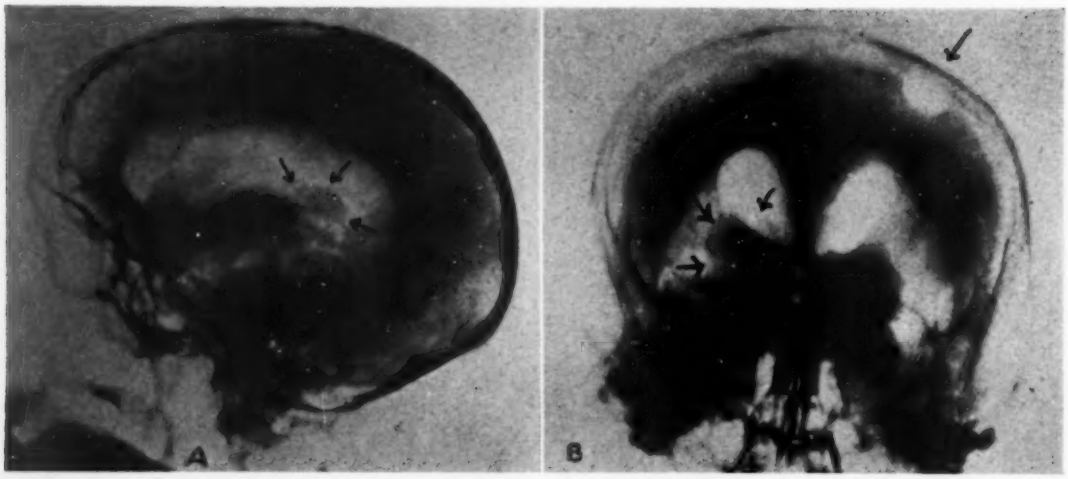


Fig. 4. Large abnormal glomus defect measuring 700 sq. mm. present on the side contralateral to the trephine opening for ventriculography and due to cysts of the glomus choroid. *A*, in the lateral view and *B*, in the sagittal view.

or absent, it may occasionally be possible to visualize in the sagittal views the portion of the choroid plexus just rostral to the glomus as it lies in the floor of the lateral ventricle. It projects up into the lumen of the ventricle, demarcating the thalamus which is lateral, from the body of the fornix, which is medial.

Dyke and Davidoff's average measurement of the defect produced by the glomus in the lateral horizontal views was 60 sq. mm. The maximum measurements they

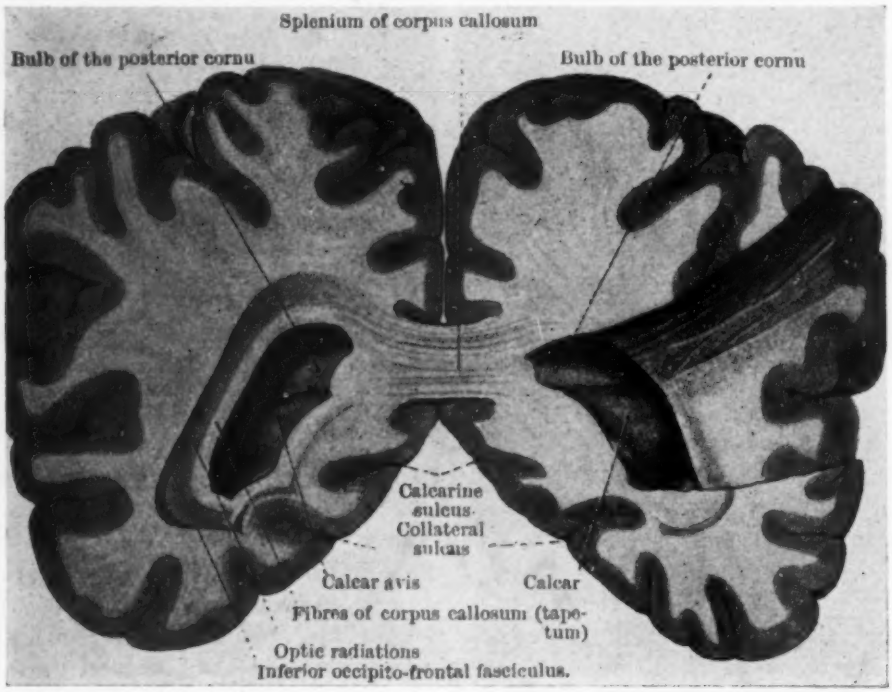


Fig. 5. Frontal section through the posterior horns of the lateral ventricles viewed from the front. (From Cunningham's Textbook of Anatomy, revised fifth edition.)[4]

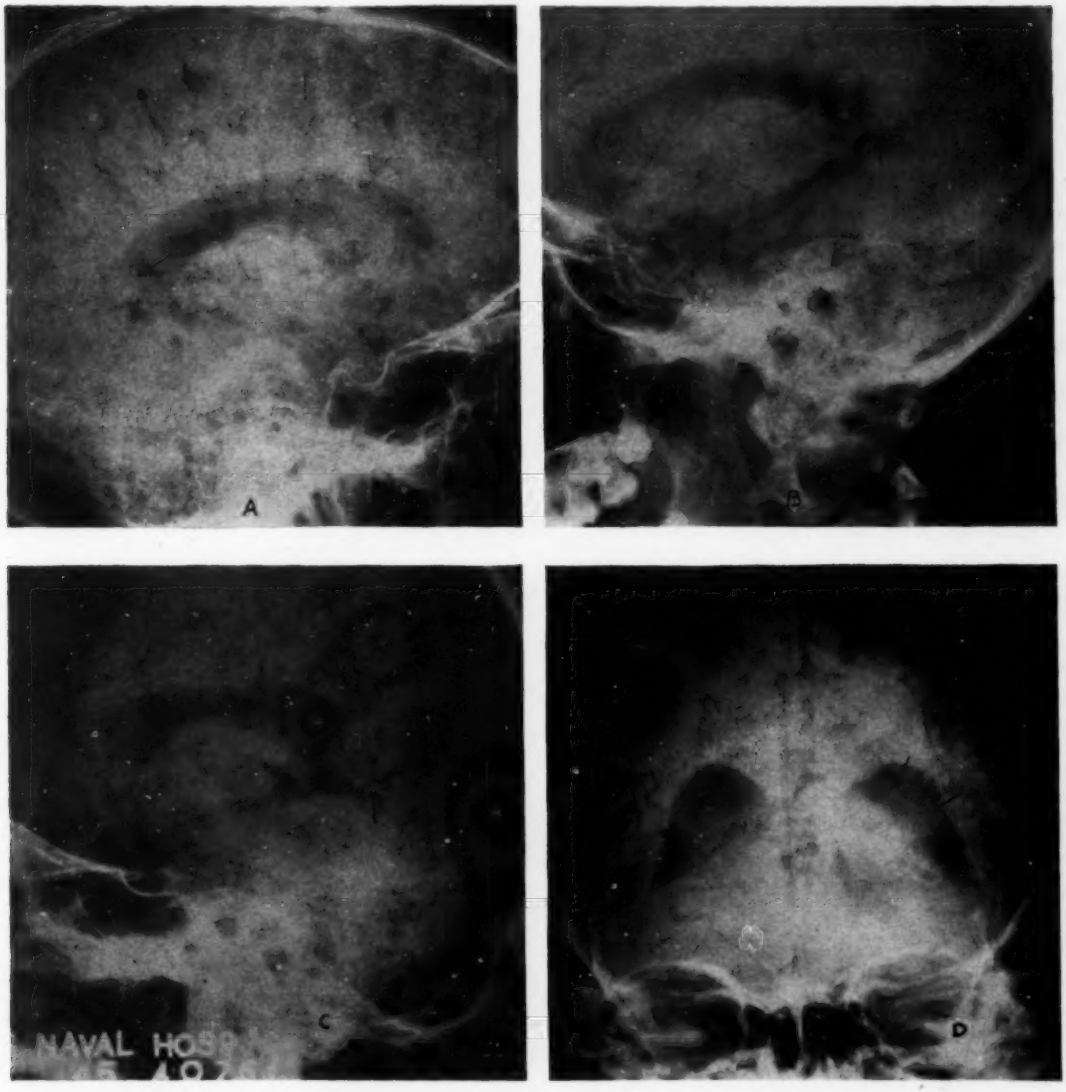


Fig. 6. Calcar avis defects. *A*, moderate sized; *B*, slightly larger than *A*; *C*, very large, measuring 381 sq. mm.; *D*, same case as *C* seen in the sagittal view.

considered within normal limits were 15 by 15 mm. (225 sq. mm.)

In 1935, Dyke, Elsberg and Davidoff demonstrated the following: (1) That "During the puncture of the ventricles in the posterior parietal region for the introduction of air, as ordinarily done, the brain cannula may accidentally come into contact with and traumatize the glomus of the choroid plexus or a vessel in the wall of the ventricle. This may produce a hematoma or edema . . . which can be recognized on the roentgen films as a defect in the outline of the lower wall of the lateral ventricle situated in or near the position of the glomus." (2) That "this enlarged defect was never produced if encephalography was done." (3) That "Whenever doubt exists as to whether the defect is due to a traumatic lesion or to some other cause, encephalography may be done a week later to clarify the point, for a traumatic lesion will then have largely disappeared." (4) That "in one case, an enlarged defect on the side

contralateral to the ventricular puncture was proven to be due to retention cysts of the glomus of the choroid plexus as shown at necropsy."

In 1938, one of the authors (M.H.P.) recorded a second case of an enlarged glomus defect (700 sq. mm.) present contralateral to the side of ventricular puncture and due to cysts of the glomus.

Fron a pathological viewpoint, enlarged glomus shadows may also be caused by benign hypertrophy or by other tumors of the choroid plexus, or of the neighboring ventricular wall.

2. CALCAR AVIS INDENTURE

The second indenture or defect is known as the calcar avis defect (hippocampus minor) and is produced by an invagination of the ventricular wall in the region of the junction between the atrium and the occipital horn on the medial and slightly on the dorsal aspect of this portion of the ventricle. The invagination results from a deep projection, laterally, of the calcarine fissure which causes the fibers of the posterior forceps to detour around it, thus producing a projection or elevation into the ventricle in this region. In the course of development, the visual receptive area striata becomes folded along its axis during the sixth month, and the furrow thus formed is called the calcarine fissure. The name was applied to the fissure by Huxley because its deep anterior part indents the whole thickness of the medial wall of the hemisphere, and the swelling so produced was supposed by the older anatomists to resemble a cock's spur and was hence called calcar avis.

The indenture representing the calcar avis varies greatly in size. In some, it is absent or else shallow and insignificant. It is not necessarily the same size on both sides. It may be greatly enlarged unilaterally, and normal or absent on the contralateral side. When large, it will be found that the occipital horn is correspondingly small or absent as the size and shape of the occipital horn is dependent to a considerable extent upon the development of the calcar avis and the forceps major. Infrequently, the forceps and the calcar avis produce a distinct notch in the rostral portion of the occipital horn.

We have found the notch to average about 50 sq. mm. in the lateral roentgenograms when present. The largest normal one encountered measured 381 sq. mm. Care must be exercised not to regard this indenture as pathological but to classify it as a variation in the normal.

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CRANIAL MANIFESTATIONS OF FIBROUS DYSPLASIA OF BONE

THEIR RELATION TO LEONTIASIS OSSEA AND TO SIMPLE BONE CYSTS OF THE VAULT*

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NUMEROUS contributions to the knowledge of polyostotic fibrous dysplasia have established the fact that the skull is frequently involved in this disorder. Skull changes are often the only manifestations of the disease.

Morphological and roentgenological abnormalities in the bones of the skull are diverse. These range from small, simple translucencies and blister-like bone cysts which may be sharply outlined, rounded, or irregular in contour and measure only 2 to 3 cm. in diameter, to more extensive involvement of the calvarium and bones of the face. In rare extreme cases, intense exuberance of massive bone deposits may cause diffuse thickening of the calvarium as much as 2 to 3 cm. It may also obliterate the structures of the base of the skull, and extension of the disease into the bones of the orbit and sinuses may transform the entire skull into an almost shapeless mass. Since the end of the last century such cases have been frequently described as leontiasis ossea.

Despite the great variety of cranial manifestations accompanying fibrous dysplasia, clinical and pathological evidence is sufficiently coordinated to warrant primary investigation of the bones of the skull and face irrespective of known widespread skeletal involvement. Occasionally, skull changes are the first and only tangible evidence of this generalized disorder; misinterpretation may obscure the true diagnosis and lead to ineffective or harmful treatment. Pathological reactions of membranous bones differ from those of other types; in the skull, bone destruction and osteogenesis underlie different effects of static and dynamic influences from those in other bones.

Skull changes of fibrous dysplasia demonstrated roentgenologically do not always correspond to those in other parts of the skeleton, where broadening of the bone, thinning of the cortex, and a rarefied, trabeculated appearance of the spongy structure gives the impression of cyst formation. In contrast to these skeletal changes, there is a tendency toward formation of sclerotic, dense bony deposits in moderately advanced and severe cases. This is most marked when the disease extends to the base of the skull, paranasal sinuses, or the nasal cavity.

LIMITED INVOLVEMENT OF THE SKULL

Roentgenologically, at this stage the foci of the disease resemble simple, rounded, cyst-like translucencies of the vault, with widening of the diploe, loss of bone tissue, and thinning of the tables. These cysts may either protrude beyond the outer table, or remain level with its surface. This depends upon the extent to which the bone has expanded due to connective proliferation. Their appearance may not change during many years of observation. Frequently, they are localized in the occipital squama, but may be observed in the parietal and frontal bones as well. The cyst margins are dense, and usually faint bone spicules are seen within the cystic area. In none of our cases did the cysts pass through sutures. Thus, in accordance with the skeletal classification of the disease, they may be considered as a monostotic localization of

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fibrous dysplasia. Only once in our group of cases were skeletal changes present. No biochemical abnormalities were observed in two examined instances. No clinical signs were observed which could have been caused by the changes of the cranial vault.

MODERATE CRANIAL INVOLVEMENT

In most patients presenting moderate cranial involvement, development of the skeletal involvement. This finding is of diagnostic value, not only in the classification of cases under observation but also in the evaluation of old records in which the disease was described under a variety of terms. Bone cysts and deformities of long bones are present in about one-half of the cases and pigmentation of the skin and precocious puberty in females in about one-third.

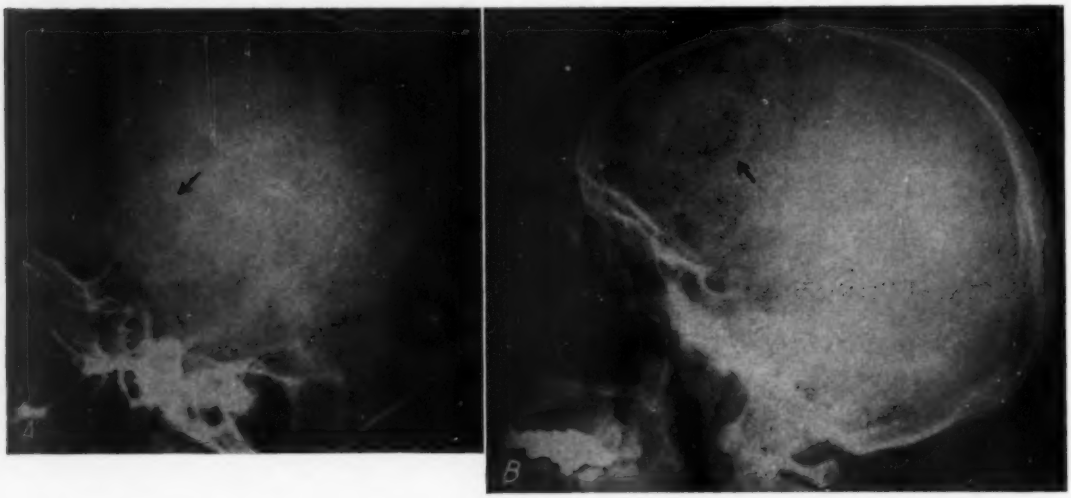

Fig. 1. *A*, one year old girl in perfect health. Small lump on right side of skull. Roentgen examination: Rounded translucency in right temporoparietal area measuring about 2 × 2 cm. Borders dense. Faint bone lamellae within density. Operation: Firm, white, brittle connective structures with small bone spicules in area of translucency. Microscopical: Dense connective tissue bounded by bony trabecula replacing bone marrow. Fibroblast-like cells arranged in whorling trabecula. Intercellular material of reticulocollagenous type. Final diagnosis: Fibrous dysplasia.

B, rounded translucency on posterior portion of temporal squama protruding on outer table. Faint bony spicules within translucency and dense bone margin surrounding translucent areas. Case studied and filed as osteitis fibrosa cystica of the skull. Normal structure of bones of calvarium. No signs of hyperparathyroidism. Roentgen diagnosis: Fibrous dysplasia. In observation for six years.

disease dates from early childhood. Already at that time deformity of the calvarium or face is evident. Areas are larger than in the stage of limited involvement. The outlines of the cranium and face are often seriously distorted. The more widespread the skeletal distribution, the more frequent and extensive the skull involvement. At this stage certain characteristic features may be most clearly recognized. First is the remarkable unilateral localization of abnormalities of the skull and facial bones. This is usually homologous to the side of the

At this stage, too, new bone formation often becomes evident; this appears on the roentgenogram as either rounded densities, irregular islands or spicules surrounded by more or less extensive translucencies.

SEVERE CRANIAL INVOLVEMENT; LEONTIASIS OSSEA (FIBRODYSPLASTIC TYPE)

All severe cases of fibrous dysplasia of bone reveal changes in the skull. In extensive involvement of the skeleton, skull changes are correspondingly serious. The circumscribed cystic expansion of the outer

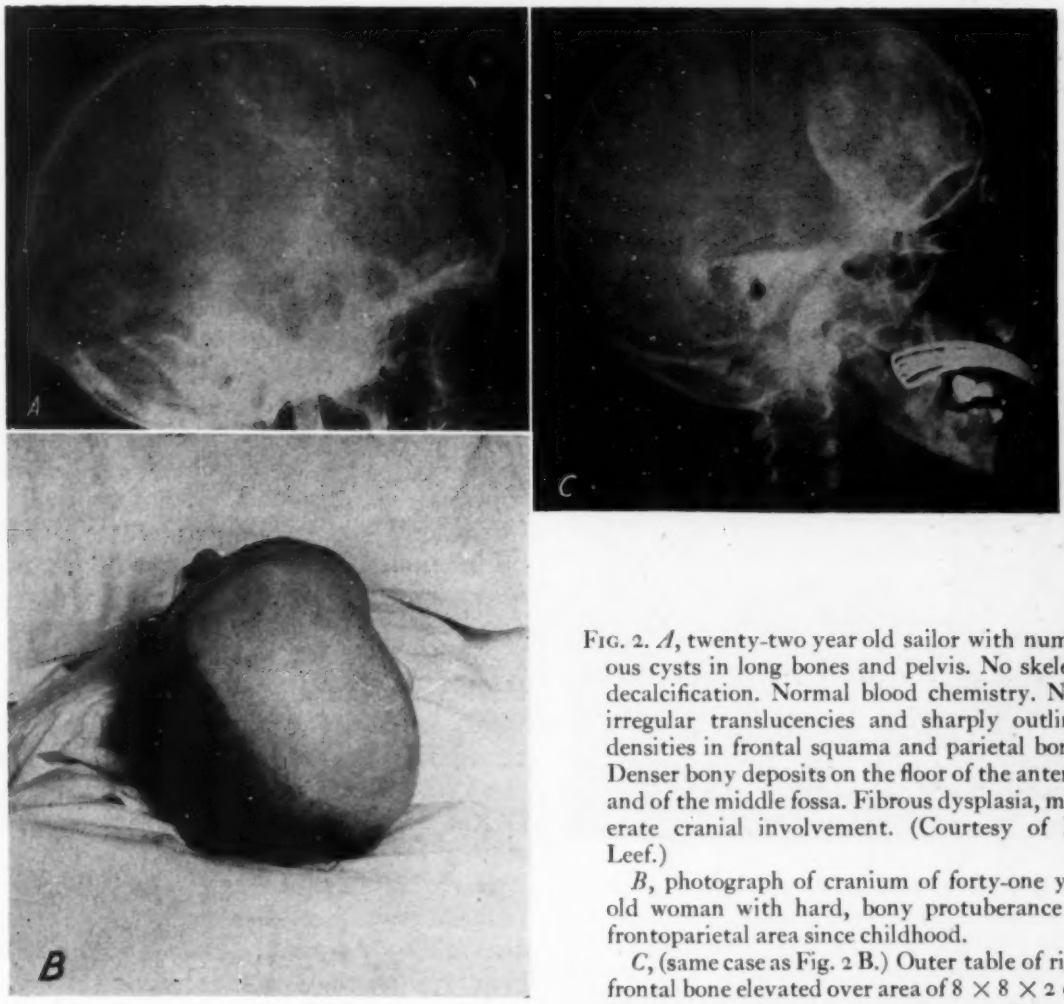

FIG. 2. *A*, twenty-two year old sailor with numerous cysts in long bones and pelvis. No skeletal decalcification. Normal blood chemistry. Note irregular translucencies and sharply outlined densities in frontal squama and parietal bones. Denser bony deposits on the floor of the anterior and of the middle fossa. Fibrous dysplasia, moderate cranial involvement. (Courtesy of Dr. Leef.)

B, photograph of cranium of forty-one year old woman with hard, bony protuberance on frontoparietal area since childhood.

C, (same case as Fig. 2 B.) Outer table of right frontal bone elevated over area of 8 × 8 × 2 cm. Note translucencies and numerous small irregular masses of ossification. Inner table of frontal bone and roof of the orbit irregular. Case diagnosed roentgenologically: Meningioma. Histopathologically: Fibrous dysplasia.

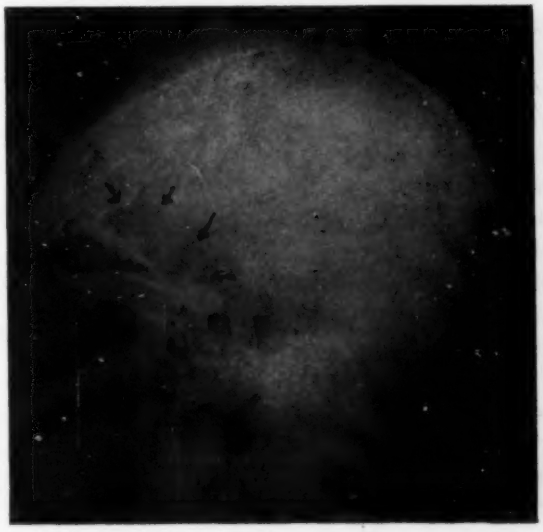

FIG. 3. Massive bony deposits on outer and inner tables of frontal squama and roof of orbits. Considerable thickening of anterior clinoids and translucencies in frontoparietal area. Diagnosis: Fibrous dysplasia. (Observed for eight years.)

table is not simila.ly pronounced. The deformity is usually not delimited; larger areas, and occasionally the whole skull, may become involved. Extensive translucencies may occur, often largely filled by irregular, sclerotic islands and dense spicules, and the entire cranium may be considerably deformed. New-formed bone masses may be deposited on the calvarium and base of the skull, especially about the

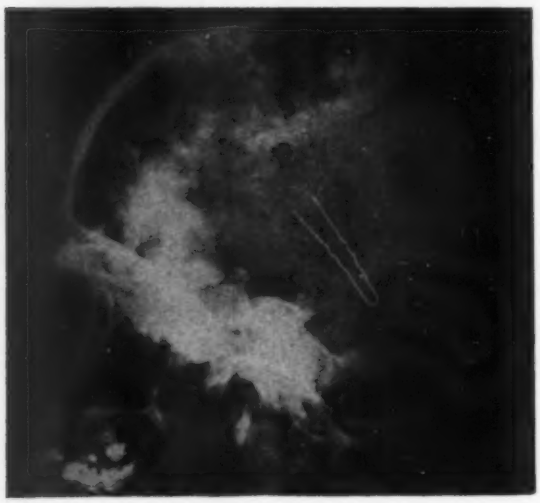

Fig. 4. Female, aged forty-one. Severe cranial involvement of fibrous dysplasia. Appearance like that of leontiasis ossea. Note extensive densities and translucencies in frontal squama. Obliteration of frontal and ethmoidal sinuses and nasal cavity. Displacement of right orbit.

sella turcica. The roofs of the orbit, the wings of the sphenoid bones, and the anterior and posterior clinoids are characteristically transformed into sclerotic bone masses. Later, the sinuses and nasal cavity also become filled with dense bone. The slow but apparently relentless proliferation of newly formed osseous tissue may displace the entire orbit with its contents, usually downward and outward, and proptosis may develop. The malar bones may protrude and the entire facial skeleton become deformed. Such bone deformities are associated with marked changes in facial appearance, sometimes to the extent of fearful disfiguration: protrusion of the cheeks, displacement of the orbits, bulging of the forehead, and an immobile, mask-like expression.

DISCUSSION

Classification of the cranial manifestations of fibrous dysplasia is somewhat more complicated than that of the skeletal changes. The present nomenclature includes several large groups of bone disorders which are probably identical to fibrous dysplasia. These have been described variously as "osteitis fibrosa cystica" or "fibrocystic disease" of the calvarium, certain forms of "hyperostosis cranii," "hemicranioses" (Brissaud et Lereboullet), "leontiasia ossea," "juvenile Paget's disease," "unilateral von Recklinghausen's disease of the skull," and so forth. It would be futile to try to identify with accuracy all old cases and names of this disease which appear in literature. Most reports contain no biochemical records of skeletal surveys, which would have provided the chief distinguishing features. Only occasionally are the older roentgenographical and pathological descriptions and illustrations helpful.

In the "prehistoric" references at my disposal, the earliest description of a skull affected by fibrous dysplasia, recorded as leontiasis ossea, is cited by Bardenheuer and Lossen. This case went into literature as one of the earliest observations of leontiasis ossea. The skull revealed enormous thickening of the vault and bones of the face. Large holes containing heavy spicules and irregular, wart-like, bony deposits were present in the thickened bones which were brittle but very hard. In von Recklinghausen's original description, his Case 5, a woman, aged sixty-six, with hyperostosis of the skeleton revealing a cyst in the occipital squama, is listed by Albright as a case of fibrous dysplasia. After a thorough study of the report of this case, I likewise am of the opinion that it is identical with fibrous dysplasia of the vault, because the bony walls of the cystic deformity were formed of compact, dense, hard, bony tissue. (In hyperparathyroidism, von Recklinghausen,

the bones are so soft they can be cut with a knife.) The celebrated specimen of the Musée Dupuytren is probably another case of fibrous dysplasia, revealing large bony cysts of the vault associated with increased thickness and density of cranial bones. (For figure, see Cushing and Eisenhardt's monograph.)

In later years, Schüller collected many records of the known cases of "cranial hyperostosis." According to his description, certain cases of this disorder, and also of osteitis fibrosa cystica of the skull, hemicraniosis (Brissaud et Lereboullet), and hemihypertrophy of the skull and face associated with unilateral skeletal disease, must now be considered as fibrous dysplasia.

A wealth of information is contained in an article by Reiss who described all published cases of leontiasis ossea to 1935. In my estimation more than one-third of these cases conform to cranial localization of fibrous dysplasia. Mostly, they are characterized by their onset in childhood and the presence of homologous unilateral cranial and skeletal deformities. Kienböck, who attempted a critical evaluation of the old references concerning leontiasis ossea, collected quite a number of cases which he called "von Recklinghausen's type" of leontiasis ossea. Cysts were present in the bones of the skull and face, but no biochemical changes typical of hyperparathyroidism were discovered. Many of these old cases likewise must be classified with the fibrous dysplasia group. More recent case reports and references appear in articles by Furst and Shapiro, Lichtenstein and Jaffe, Sternberg and Joseph and others.

CLINICAL ASPECTS

Fibrous dysplasia of bone is primarily a disease of childhood, but because of its protracted course, the condition is not encountered medically until adolescence or adult life. It is more frequent in females. Onset is insidious, progress slow, and the deformity becomes manifest only at the height of the disease unless early signs are discovered accidentally by roentgen examination.

General clinical symptoms and biochemical and roentgenological findings in the skeleton have been frequently described, emphasis being placed on the characteristic bone changes with their resultant cranial and skeletal deformities. Endocrine disturbances, precocious puberty in females, occasionally hyperthyroidism, and cutaneous pigmentation are present in about one-third of the cases. Recently, concomitant cardiovascular and renal disorders have been reported. The clinical entity is also known as Albright's syndrome.

Concerning cranial involvement, clinical changes consist of focal symptoms resulting from occasional local cortical irritation and displacement of adjacent structures. In advanced cases, narrowing of the cranial cavity and of the nerve canals is often associated with clinical symptoms. Generalized endocranial pressure causes increase of headaches, mental deterioration, and impairment of vision and smell. Obliteration of openings of paranasal sinuses, tear ducts, and nose often causes inflammatory changes and upper respiratory infections. Edentulous jaws are common in such condition. Progress of the disease in the skull seems to stop with the termination of normal bone growth or with puberty. It is reasonable to believe that the common clinical history of sinus disease prior to the beginning of facial deformities may be the result and not the cause of early bone changes, as it was often believed. Biochemically, in contrast to von Recklinghausen's disease, the calcium and inorganic phosphorus content of the blood is average. Occasionally, phosphatase is slightly increased. In severe cases, serum and urine calcium may be somewhat elevated.

HISTOPATHOLOGY

The primary histopathological change seems to be the transformation of rather extensive areas of bone marrow into connective tissue, following severe bone destruction by osteoclastic activity and lacunar

Fig. 5. Photomicrograph (×20) of tarnssection of thickened, deformed calvarium (same case as Fig. 2, *B* and *C*). Thin, cortical area at top is formed by lamellated normal structured bone of periosteal origin. Cortical bone layer (center) extends into diploe where it fuses with new-formed metaplastic, poorly calcified non-lamellated bone spicules imbedded in fibrous tissue. Two large holes below cortical layer are filled with connective tissue, revealing retrogressive changes. The lower part of the section shows dense bony islands consisting of meshwork of newly formed, metaplastic, non-lamellated bone surrounded by connective tissue.

resorption. Connective structures may exhibit signs of growth. In this connective tissue primitive non-lamellar or woven bone is formed, which may either remain uncalcified, or be transformed into calcified irregular lamellar bone. Telford first described the presence of hyalin cartilage in skeletal "osteitis fibrosa" (fibrous dysplasia). Sternberg and Joseph found no cartilage in skull changes. Histopathological skull findings are described by Trauner ("hyperostosis"), Lichtenstein and Jaffe, and others.

MICROSCOPICAL STRUCTURES OF ROENTGENOGRAPHIC TRANSLUCENCIES

Radiolucent areas visualized in fibrous dysplasia are the result of replacement of lamellar bone by connective, osteoid and non-lamellar bone tissues. The tela ossea is gradually destroyed from the fibrous marrow. The connective tissue tends to proliferate, and by lacunar erosion and osteoclastic activity the adjacent bone lamellae becomes resorbed. At the same time, due to periosteal activity, new lamellar bone tissue is formed on the outer surfaces of the focus through which the bony outlines become elevated, and a "cyst" is formed. Various amounts of primary, irregular, uncalcified, or poorly calcified trabeculae become visible within the connective tissue. They form an irregularly woven felt-work which supports the outer and inner tables. The connective matrix consists of numerous spindle-shaped, regu-

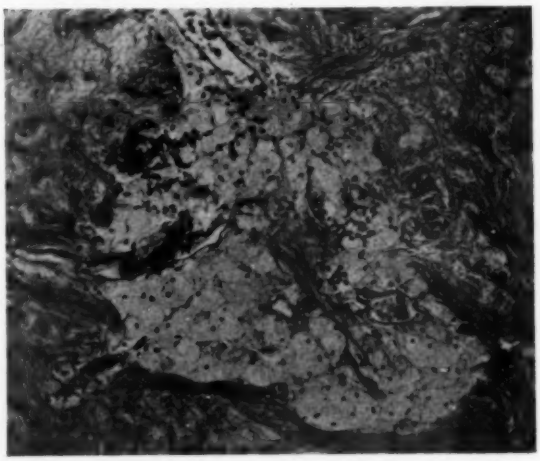

Fig. 6. Photomicrograph (×250) showing group of xanthoma cells surrounding blood vessels. Cells large, cytoplasm translucent, nuclei small and localized peripherally. No fat stains available to determine probable fat content. Note many interstices and few nuclei in connective tissue. Xanthoma cells originate from adventitial cells of blood vessels, contain products of retrogression of previous tissue structures (fat from bone marrow?).

larly stained cells and intercellular fibers distributed in bundles, rows, and sometimes in whorls. They may undergo different metamorphoses. The collagenous interstices may increase in number, whereas the number of cells may decrease. Occasionally, microscopical structures result, not unlike fibroma, with prevailing connective collagenous interstices and very few cells; or varying degrees of retrogressive change as the newly formed metaplastic primary bone lamellae.

MICROSCOPICAL STRUCTURE OF RADIOPAQUE AREAS

The radiopaque areas are consistent with newly formed and in early stages inadequately calcified osseous tissue. This seems to be formed, not by osteoblastic activity, but by metaplasia of already existing con-

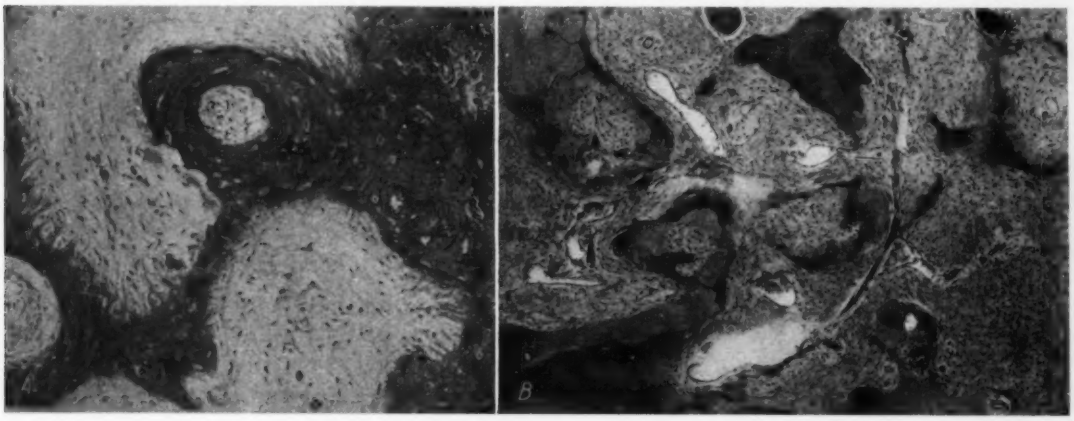

FIG. 7. *A*, photomicrograph (×250) shows metaplastic bone formation in connective tissue replacing marrow. Brushlike outlines of bone trabeculae indicate homogenization of connective fibers and their fusion into osteoid tissue. Transformation of connective tissue cells into bone cells is shown in the margin of bone trabeculae on the right.

B, photomicrograph (×250) reveals different phases of bone formation within osteoid tissue. Wide "pink" areas outside bone lamellae show osteoid tissue. In center of "pink" areas, more bluish stained, sharply outlined meshwork of well calcified, irregular lamellated bone tissue, showing erosion from within. Connective tissue reveals numerous capillary blood vessels.

may occur. Cell nuclei and fibers may disappear and a meshwork of cystic holes of different sizes and shapes may replace the connective structures. These spaces are filled with faintly eosinophilic, granular material. Occasionally, small groups of xanthoma cells are visible in the vicinity of blood vessels, indicating resorption of fatty material from the tissue of the dysplastic focus. Snapper and Parisel believed that the presence of xanthoma cells indicated that the whole pathology might be a secondary modification of xanthomatous change. This theory has since been disproved by several authors.

Bone destruction within the translucent areas involves the old, normal bone as well nective tissue. Homogeneous substance is deposited between the connective fibers, and gradually the connective tissue cells become enclosed in cell spaces to form the bone cells. Later, calcium salts are deposited in the newly formed matrix. The primitive bone, when first formed, shows ill defined, brush-like margins. Many sections remain uncalcified; some of them are gradually replaced by lamellar bone. The transition from normal bone into primary pathological structures is not sudden. Organized bone lamellae are surrounded by osteoid structures which are embedded in a connective matrix. Findings are similar to those which occur in inflammatory conditions where woven bone is formed on the

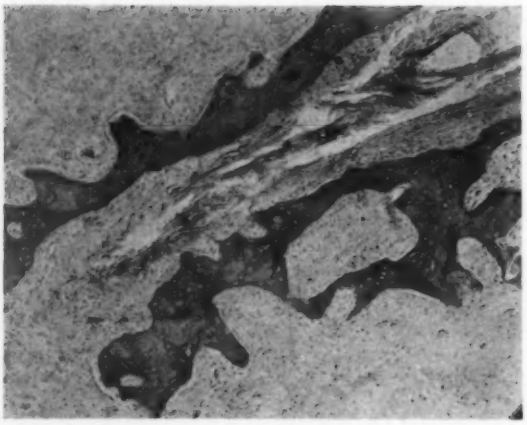

Fig. 8. Photomicrograph (×150). Oblique section of blood vessel surrounded by well calcified sheath of non-lamellated bone. Note connective tissue replacing bone marrow.

surface of lamellar bone. This indicates that the surface of lamellar bone has undergone some osteoclastic erosion. It is remarkable that newly formed bone trabeculae as well as osteoid tissue are often localized in surroundings of blood vessels. Lamellar bone structures ("blue" in hematoxylin-eosin stains) are narrower and smaller than the woven, non-lamellar structures ("red" in same stains). Some of them run parallel to the surface and serve to reinforce the structure of the vault. Occasionally, at the edge of the lesion, a single trabecula may form the demarcation between normal marrow and dense, fibrous tissue. Ossification is more extensive where the mechanical stress is greatest, such as at the base of the skull.

The fate of this newly formed bone tissue is various. Some lamellae may again be destroyed by lacunar resorption and osteoclastic activity; others seem to remain as a more or less permanent part of the tissue structure.

Periosteal bone formation occurs in the vicinity of expanded foci of dysplasia, furnishing the bone shells around connective tissue. The original periosteal bone is also decomposed and again regenerated, and the process is repeated as long as small residues of the periosteal bone are present.

ROENTGEN DIAGNOSTIC ASPECTS

The roentgenological diagnosis of fibrous dysplasia of the skull is based on the morphology of bone changes. It seems that the distribution, extent and appearance of the newly formed bone tissue follow specific rules. These are influenced by the vascularization of connective tissue and by the statics of the cranium which differ from those in other parts of the skeleton. The base of the skull, which is subjected to

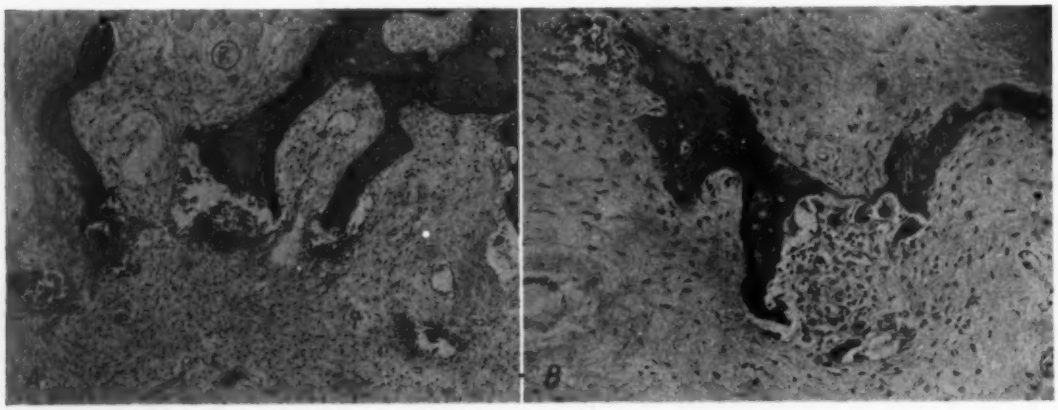

Fig. 9 *A*, photomicrograph (×150). Irregularly distributed, poorly calcified non-lamellated bone revealing destruction in semicircular area at border of larger masses of connective tissue. Area of bone destruction shows marked hyperemia; red blood corpuscles outside wall of capillary blood vessels. At left, note several osteoclasts in Howship's lacunae at margin of destructive processes.

B, photomicrograph (×250). Irregular, small, newly formed and poorly calcified metaplastic bone spicule shows an area of destruction with numerous osteoclasts and highly vascularized connective tissue.

greater stress than the calvarium, produces more bone tissue. Consequently, it is dense in roentgenograms. Later, however, this tissue grows not only according to its adaptation to static principles, but also as a result of intrinsic factors of osteogenesis. Bone formation, often following the course of the greater blood vessels and their well defined borders, produces sharply outlined densities. In roentgenograms, these alternate with translucent areas of connective or non-calcified osteoid tissues. The presence of dense bone spicules and alternating clear, translucent areas of ground glass quality are characteristic roentgenographic findings. Visualization of them permits not only the correct diagnosis to be made but differential diagnostic considerations of cranial manifestations of roentgenologically similar systemic bone diseases as well.

In von Recklinghausen's disease, cystic changes in the skull are associated with characteristic, diffuse, granular decalcification of the entire cranium. Consequently, if the general background remains normal in appearance, the cystic changes cannot be considered von Recklinghausen's disease. In xanthomatosis, Schüller-Christian's disease, and other reticulo-endothelial disorders, no true cysts are observed. Defects of the vault do not possess their own bony wall; they are simple, large, sharply outlined, and often multiple holes. In both von Recklinghausen's and Schüller-Christian's diseases, the clinical picture is entirely different from that of fibrous dysplasia.

Solitary xanthomas and other bone defects of the skull do not produce appreciable amounts of bone; consequently, as a rule, they do not reveal internal bone structures.

In Paget's disease, the margins between normal and transformed bone are mostly not sharply outlined; transition is continuous. The cotton wool appearance of the bones of the skull in Paget's disease usually reveals rounded, indistinctly outlined densities. They are surrounded by coarse, trabeculated residuals of spongy structures of the diploe. Larger, ground glass-like translucencies are absent. In addition, the disease produces a relatively uniform thickening and, in advanced cases, characteristic enlargement of the cranial vault. This seems to be the result of softening of the newly formed Paget bone. It involves large

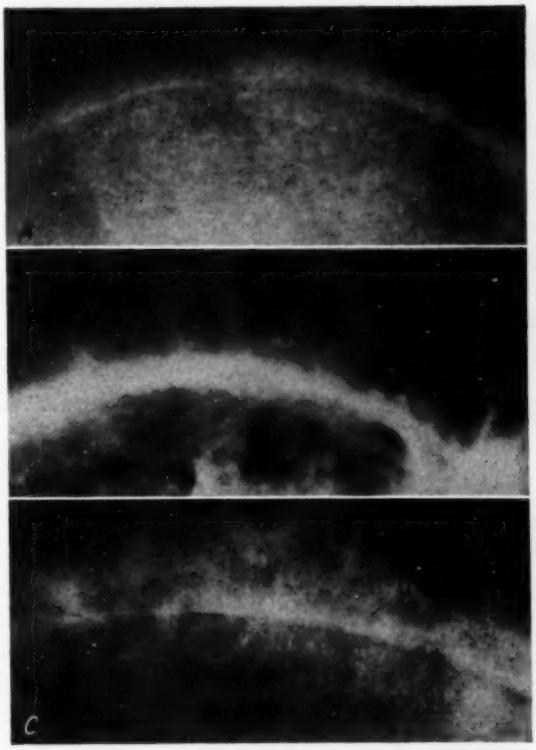

Fig. 10. *A*, roentgenogram of vault in hyperparathyroidism (×2). Note thickening of diploe. Inner and outer tables have almost entirely disappeared; diploic structure replaced by decalcified coarsely granulated bone tissue surrounded by faint, almost point-like meshwork of more translucent areas. No large islands of newly formed bone tissue; no cystic changes.

B, part of cranial vault in fibrous dysplasia. Densities more sharply outlined, no "cotton-wool appearance", but irregular masses and spicules of extremely dense bone tissue. In contrast to Paget's disease, large holes appear which do not contain spongy structures. Inner table much denser. Outer table has disappeared and structural changes mainly involve area of diploe.

C, part of cranial vault in Paget's disease (×2) revealing thickening of bones with fuzzy outlines. Rounded densities surrounded by translucent areas which contain coarsely trabeculated spongy structures. No hole formation evident in Paget's disease. Inner table very thin. Outer table has disappeared entirely, and structural changes involve regularly expanded diploe.

areas of the cranium. Usually, there is no circumscribed bulging or expansion of the bones. If the entire cranial vault is involved by Paget's disease, the roentgenological changes are so characteristic that they cannot be confused with the irregular, sharply outlined spicules, densities, and cyst-like translucencies of fibrous dysplasia.

It is important to distinguish the foci of fibrous dysplasia from bony reactions occurring around meningiomas. In moderate or severe cranial involvement, the deformity of the skull is so characteristic that it cannot be confused with circumscribed hyperostosis occurring in meningioma. Bony reactions of meningiomas are progressively growing, solid thickenings of the vault. Destructive bone lesions caused in rare instances by meningiomas are, in contrast to foci of fibrous dysplasia, not surrounded with continuous bone margins. Fibrous dysplasia starts in early youth. Bony reactions of meningiomas occur, as a rule, in adults. They involve first the inner table; diploe and outer table are changed later. In fibrous dysplasia the diploe is the primary localization of the disease.

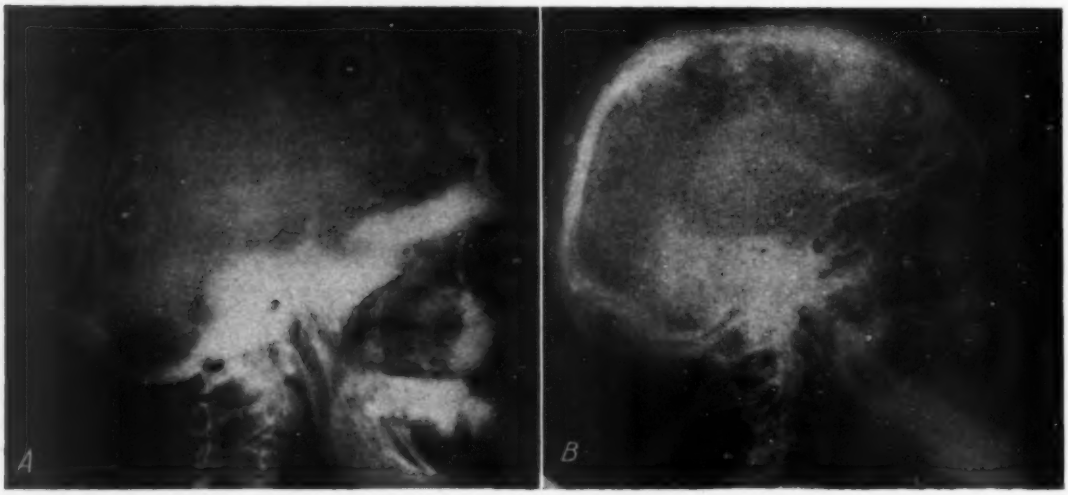

FIG. 11. *A*, "leontiasis ossea" due to Paget's disease. Forty-five year old woman with extensive skeletal involvement. Note thickening of anterior wall of maxillary sinus, alveolar process, and base of skull. Paget structure of frontal squama.

B, "leontiasis ossea" due to Paget's disease of the mandible and calvarium. Sixty-four year old nurse with skeletal Paget's disease. Mandible almost twice as large as normal.

RELATION OF FIBROUS DYSPLASIA TO LEONTIASIS OSSEA

According to the present extent of our knowledge, we must distinguish three types of leontiasis ossea, namely, Virchow's type, Paget's type and von Recklinghausen's type. The frequent incidence of fibrous dysplasia of the skull prompted me together with W. Cutting to review this problem. Our studies convinced us that the majority of cases described as Virchow's, and especially as von Recklinghausen's type of leontiasis ossea, which showed no signs of diffuse osteoporosis and no biochemical abnormalities, were synonymous with fibrous dysplasia. Roentgenograms appearing in such communications can sometimes be identified as typical pictures of fibrous dysplasia. In a recent publication, we segregated cases of leontiasis ossea caused by fibrous dysplasia and classified them as "fibrodysplastic type" of leontiasis ossea. In the current literature, cases of Freedman, Gemmel, Case 1 of Hodges, the case of Kirkland, Case 3 of Kienböck, all described as leontiasis ossea, seem to be identical with fibrous dysplasia of the skull.

In a recent publication, Pugh also emphasized the close relation of fibrous dysplasia of the skull to leontiasis ossea. He thought that this relationship might be the explanation of leontiasis ossea. I have already pointed out that according to available information, fibrous dysplasia is the most frequent but not the only cause of leontiasis ossea. Second in frequency is Paget's disease of the bones of the face. The

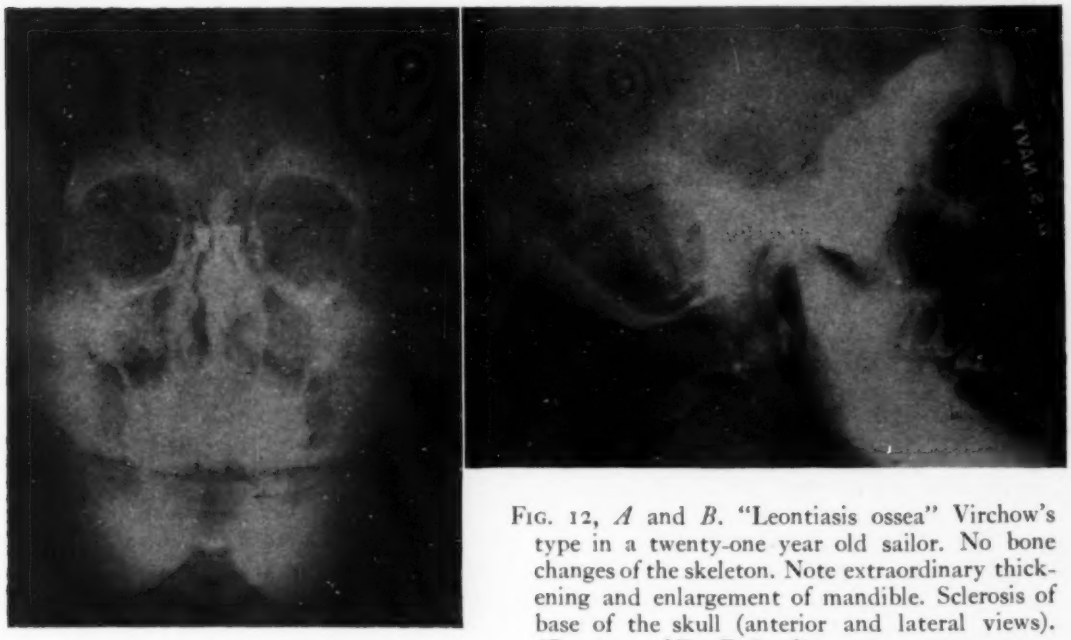

Fig. 12, *A* and *B*. "Leontiasis ossea" Virchow's type in a twenty-one year old sailor. No bone changes of the skeleton. Note extraordinary thickening and enlargement of mandible. Sclerosis of base of the skull (anterior and lateral views). (Courtesy of Dr. E. Leef.)

original Virchow's type seems to be one of the rarest of all conditions leading to leontiasis ossea. Unexplained remain also cases of massive diffuse bony deposits on the facial skeleton showing roentgenographic density of marble bones. Such cases are occasionally associated with skeletal changes similar to melorheostosis (Franklin and Matheson).

RELATION TO SIMPLE BONE CYSTS OF THE CRANIAL VAULT

Circumscribed small translucencies of the cranial vault are a relatively frequent roentgenographic finding. As previously mentioned, small foci of fibrous dysplasia may produce circumscribed translucencies not unlike small inflammatory changes or tumor metastases. Usually, these small cysts are located in the occipital squama, but occasionally appear in the parietal and frontal. Biopsy findings of two of such small, sharply outlined, rounded translucencies with relatively dense borderlines and of a third case representing a larger, oval, blister-like cystic translucency above the orbit, revealed that they consisted of holes within the diploe. They were outlined by shiny connective membrane. In all 3 cases, the meninges and portions of the cerebral cortex had prolapsed into the holes. In one case, the cyst wall itself was formed of dense bone layers with hardly any fibrous change in the small marrow cavities. The bone layers were irregular in build. In one case, irregular structures of partly nonlamellated bone were observed; ossified bone spicules ended abruptly at the level of the connective membrane outlining the border of the hole. In the third case (cyst above the orbit), no bone particles were examined; however, the cyst contained, in addition to brain tissue, small amounts of spindle-shaped connective tissue cells with

collagenous interstices in whorls and bundles.

The histogenesis of these holes is difficult to interpret. It is possible that the holes represent degenerated and resorbed areas of fibrous dysplasia, in which the inner table has become entirely atrophic and the meninges and parts of the cortex prolapsed into the space previously occupied by connective structures of fibrous dysplasia. (See also case of Neller.) In only one of our cases was such a metamorphosis likely. This showed abruptly ending and somewhat irregular and partly incompletely ossified non-lamellated bone structures with some fibrous changes in the bone marrow. Other possibilities in explanation of the origin of these cysts, namely tissue malformation, degenerated fibromas, xanthomas, and so forth, cannot be excluded.

Fig. 13. Male, aged sixty-eight. Triangular bone defect in left parietal bone surrounded by slightly denser bone structures. No change in appearance during two years' observation.

COMMENTS AND SUMMARY

It has been pointed out that fibrous dysplasia of bone frequently involves the skull. The extent of cranial manifestations is related to the extent of the involvement of other parts of the skeleton. Roughly, in 10 cases of monostotic skeletal involvement, one cranial case has been recorded. In moderate skeletal involvement, about half the cases show skull changes. In severe skeletal disease, the skull participates constantly. Occasionally, the skull shows the only manifestations of the disease, whereas no skeletal changes and no clinical findings of related endocrine disturbances are encountered.

Pathological and roentgenological evidence of foci of the disease are in limited cranial manifestations—small, simple, cyst-like bone blisters in the vault. In more advanced cases, localized deformities with translucencies and densities within the deformed areas are observed. In later stages, extensive, dense, bony islands and spicules become visible in the expanded parts. In severe involvement, the entire vault, the base of the skull, and the facial skeleton are deformed. Bone deposits are maximal and localized mainly at the base of the skull and in the face.

Prior to the segregation of fibrous dysplasia from related conditions, misinterpretations were frequent. They were classified and denominated as cranial hyperostosis or, if localization was unilateral, as hemicraniosis, hemihypertrophy, unilateral hyperostosis, unilateral von Recklinghausen's disease, osteitis fibrosa cystica of the skull, or von Recklinghausen's disease, and so forth. Most of the advanced cases, however, have been reported as leontiasis ossea. There are indications that skull specimens known as leontiasis ossea since the last century were actually fibrous dysplasia.

The basic tissue change is replacement of the diploe by connective structures (visualized roentgenographically as translucencies) in which irregular, poorly or completely ossified, non-lamellated bone tissue may develop (visualized as densities). In advanced cases, these densities are in the foreground and the bone changes may show diffuse areas of increased density. This is especially characteristic at the base of the skull. Detailed roentgenological analysis of the appearance of the fibrous dysplasia usually permits recognition and denomi-

nation of this condition and its differentiation from von Recklinghausen's disease, Paget's disease, and xanthomatosis. Segregation of skull changes from localized bone reactions caused by meningioma is of great practical importance.

Localized clinical symptoms caused by fibrous dysplasia of the skull are present in cases of severe involvement. General symptoms are identical with those of Albright's syndrome. A skeletal and clinical survey of each case presenting cranial manifestations of this disorder is an urgent necessity.

I am indebted to Drs. Alvin C. Cox and H. W. Carnes of the Department of Pathology, Stanford University School of Medicine, for placing microscopical slides at my disposal. I am also indebted to Dr. Edward Leef of the Department of Radiology for Figures 2*A* and 12.

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PULMONARY EMPHYSEMA AND TUBERCULOSIS*

A ROENTGENOLOGICAL AND PATHOLOGICAL STUDY

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PULMONARY emphysema as a sequel and complication plays an important part in the course of all forms of pulmonary tuberculosis. Every physician who comes in contact with tuberculous patients knows how frequently bronchitis, asthma, and emphysema are diagnosed as the primary disease in patients who have had pulmonary tuberculosis for many years. In such cases signs and symptoms of non-tuberculous pulmonary disease must be considered as phenomena secondary to tuberculous lesions in the lungs. Emphysema associated with pulmonary tuberculosis is as manifold pathologically as in other chronic pulmonary diseases which are characterized by fibrosis, destruction of lung tissue, and especially by endobronchial changes.

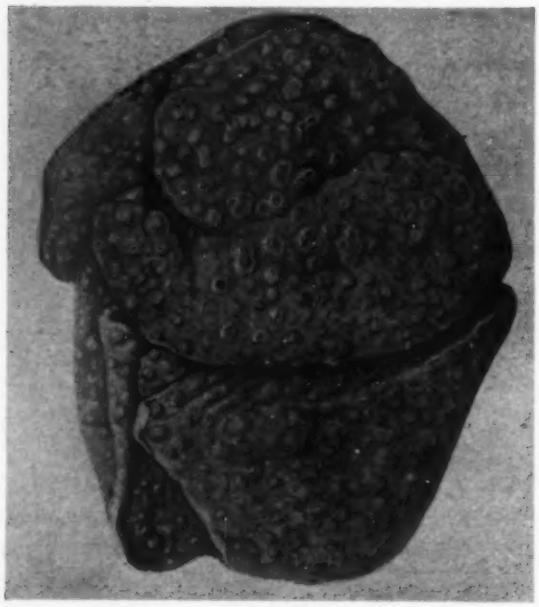


FIG. 1. Lung specimen of progressive miliary tuberculosis. Intrafocal emphysematous blebs (from Pagel[7]).

The purpose of this study was to investigate the various forms of emphysema in pulmonary tuberculosis and to classify them on the basis of morphology and pathogenesis. It is felt that the term "compensatory emphysema" should be limited to those cases which do not show definite bronchial changes.

MORPHOLOGY OF EMPHYSEMA IN TUBERCULOUS LUNGS

In discussing the various pathological features of emphysema in tuberculosis, it is necessary to differentiate between (1) the individual tuberculous lesion, and (2) the stage or phase of tuberculous disease.

In the majority of cases of pulmonary tuberculosis, the emphysematous changes are not diffuse, but are localized in the area and in the immediate vicinity of the tuberculous lesions. These changes may be classified

(a) Intrafocal emphysema
(b) Perifocal emphysema
(c) Emphysematous bullae and blebs
(d) Interstitial emphysema
(e) Diffuse (compensatory) emphysema

(a) In *intrafocal emphysema* there is no doubt that bronchial and bronchiolar obstruction play the most important part. Exudate and liquefying necrotic material are present in the bronchial tree, and air is trapped within the soft lesions due to a check valve mechanism. In the pathogenesis of fresh cavities this mechanical factor is not only of great importance in determining their size, but it may influence spontaneous healing or lead to rapidly progressing tuberculosis.

* From the National Jewish Hospital at Denver, Dr. Allan Hurst, Medical Director, and the University of Colorado School of Medicine.

Small intrafocal air bubbles are limited to cases of an exudative character; in areas of perifocal inflammation, and occasionally in soft miliary tubercles in which caseation is predominant (Fig. 1). Intrafocal emphysema is not limited to tuberculosis, but is frequently found in pulmonary edema, and in bronchopneumonia. In tuberculosis it is not of great clinical significance, because it seems that in the majority of these cases the trapped air is readily absorbed or expelled, depending on the complete occlusion or complete re-opening of the bronchus.

(b) *Perifocal emphysema* is by far the most common type. Emphysematous changes are almost always present, in the immediate vicinity of fibrotic and productive lesions, and to a much lesser degree around exudative lesions (Fig. 2 and 3). In the periphery of calcific foci it is never absent, unless the calcium is deposited in solid fibrous tissue. The amount of emphysema does not parallel the size of the lesion.

Fig. 2. Perifocal emphysema with blebs in caseous pneumonic tuberculosis.

Fig. 3. Fibro-exudative and cavernous lesions. Extensive perifocal emphysema.

Frequently little or no emphysema is found near large fibrocalcific areas, while tiny calcific foci may be suspended in an extensive emphysematous region (Fig. 4).

Such discrepancies cannot be explained on the basis of a shrinkage of the original lesion alone, although we agree that a prolonged pulling on neighboring relatively normal lung tissue might lead to dilatation of alveoli and to stretching and rupture of their septa. Much more significant in the pathogenesis of perifocal emphysema is the condition of the smaller bronchi and of the bronchioli within and in the periphery of lesions while they are undergoing progressive or regressive changes. In chronic

Fig. 4. Multiple calcifications with extensive emphysema.

atelectatic and fibrotic lung tissue three characteristic changes may be found: ectasia of larger bronchi leading to the lesion, so-called alveolar hyperplasia within the fibrotic areas, and obliteration as well as disappearance of bronchioles in the entire region. It may be assumed that the bronchiolar changes come first, and that in the case of fibrosis and atelectasis their obstruction is complete and permanent. In the case of emphysema, however, the bronchi and bronchioles are never completely blocked. Their partial obstruction as outlined under (a) intrafocal emphysema may lead to overdistention of alveolar structures.

Perifocal emphysema varies in appearance from small areas of minimal distention of alveoli to large bulla-like structures, the interior of which is traversed by thin remnants of alveolar septa and obliterated capillaries.

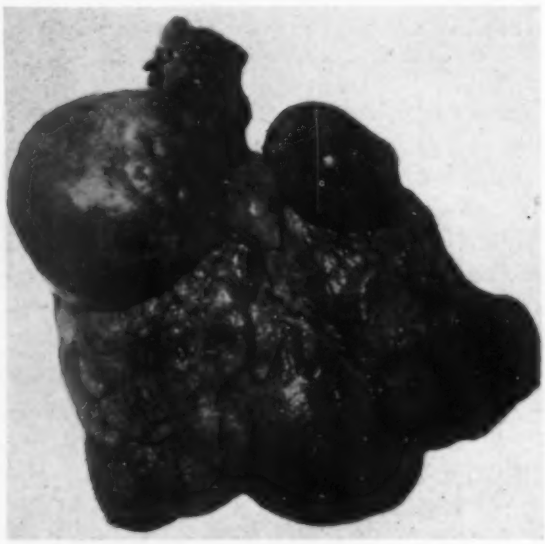


Fig. 5. Bilateral emphysematous blebs in case of fibrotic apical lesions.

Fig. 6. Emphysematous blebs with septa formed by thickened pleura.

(c) *Emphysematous bullae and blebs* have received major attention in the literature, probably not only because of their spectacular roentgenological and pathological features, but also because of their clinical

significance. On roentgen examination they must be differentiated from tuberculous cavities, penumothorax, and cysts (Fig. 5 and 6).

A bleb is formed when the lung is separated from the pleura by interstitial emphysema, the greater part of its wall consisting of attenuated visceral pleura. In bullae the pleura retains its connection with lung parenchyma, and the pleura does not take part in the formation of the bullous wall. Both bullae and blebs remain unchanged over long periods of time, or they show only insignificant changes in size and shape.

It is a generally accepted theory that no bronchi are in communication with the lumen of these structures as soon as their wall has been definitely formed. It must be assumed, however—as in other forms of emphysema—that atelectasis would develop at the site of the original emphysema, due to an absorption of the trapped air, if the regional bronchi were entirely blocked. Since this does not happen in the majority of cases, it is felt that small narrowed bronchi still penetrate the walls of bullae and blebs, allowing air to enter, but preventing it from leaving during expiration. Manometric pressure readings of large blebs in a postmortem lung still showed high positive pressures (plus 8 and plus 11 cm. of water). The bronchographic findings therefore are not conclusive; the contrast fluid probably does not enter the blebs or bullae through the narrowed bronchioles.

Emphysematous bullae and blebs are a common sight in tuberculous lungs, especially in those with fibrotic changes. While generally blebs do not show necrotic changes of their walls, aspiration of tuberculous material into their interior is possible (Fig. 7, *A*, *B* and *C*).

(d) *Interstitial emphysema* is not found very often in tuberculous lungs, except as a complication in artificial and spontaneous pneumothorax. Air is pressed into the interstitial tissue, and is found especially along the vascular structures in the interlobular septa. This form of emphysema may develop in cases of asphyxia, in whooping cough, and in severe cases of tracheobronchitis with pseudomembranes. The pearl-string arrangement of tiny emphysematous blebs in children is the classical example of interstitial emphysema.

(e) The term "*compensatory emphysema*" should be reserved for those cases in which relatively normal portions of lung tissue become hypertrophic, as the result of extensive fibrosis, necrosis, and atelectasis in other parts, with ensuing loss of respiratory surface. Compensatory emphysema always leads to pulmonary hypertrophy, but must be differentiated from senile emphysema in which the lungs are atrophic. It is relatively easy to make a differential diagnosis during autopsy. After opening of the pleural cavities, the hypertrophic emphysematous lung changes very little in size, while the senile atrophic lung collapses. Many cases of so-called compensatory emphysema, especially if limited to parts of a lobe, are not the result of compensation, but of extra- and endobronchial changes. The characteristic pathological and roentgen changes of these forms of emphysema will be discussed later.

EMPHYSEMA AND THE VARIOUS STAGES OF TUBERCULOSIS

(1) *Primary Tuberculosis.* It is very seldom that gross emphysematous changes are observed as part of an uncomplicated primary complex. The original lesion is of a pneumonic nature, and most of it undergoes resolution. As soon as the central caseous nucleus becomes calcified, perifocal emphysema may become manifest. There are cases in which the calcified Ghon focus is suspended in emphysematous lung tissue as in a spider web; this loose connection of calcified lesions with the surrounding tissue is probably the reason why in many cases such lesions are expectorated. Since the Ghon focus is most frequently located in subpleural areas, the residual emphysema is usually found in these regions. It can be assumed that many cases of spontaneous pneumothorax of so-called "non-tuberculous" origin are attributable to rupture of

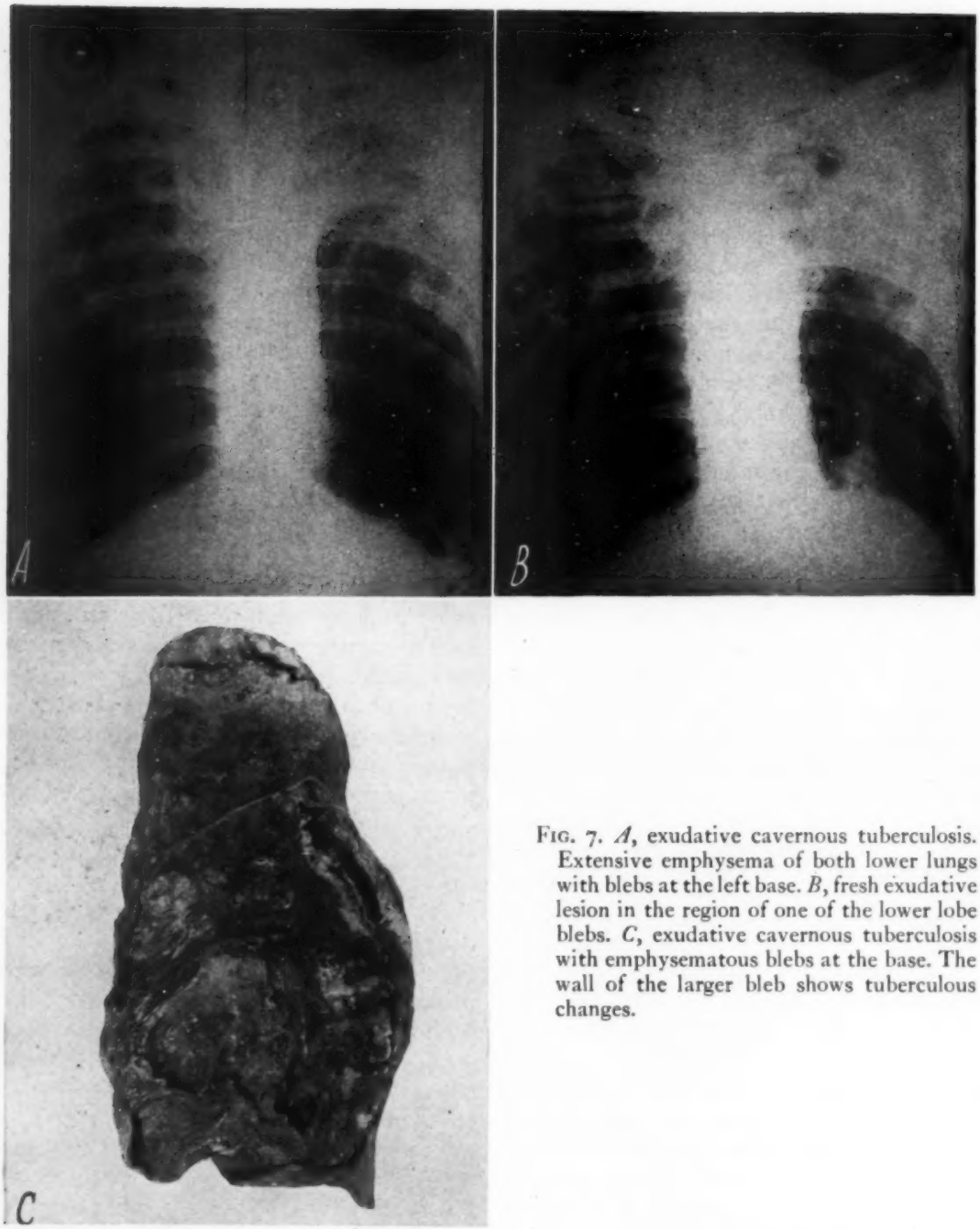


Fig. 7. *A*, exudative cavernous tuberculosis. Extensive emphysema of both lower lungs with blebs at the left base. *B*, fresh exudative lesion in the region of one of the lower lobe blebs. *C*, exudative cavernous tuberculosis with emphysematous blebs at the base. The wall of the larger bleb shows tuberculous changes.

such subpleural emphysematous lesions.

Obstructive emphysema may become part of an active progressive primary pulmonary tuberculosis if a caseated lymph node erodes through the wall of a bronchus, thus creating a valve-like mechanism. In many of these cases the emphysema is accompanied by a caseous pneumonic process. If the bronchus is completely occluded either by caseous material or by extrinsic pressure, an area of atelectasis may develop. So-called epituberculosis is probably identical with such atelectatic lesions.

(2) *Hematogenous Tuberculosis.* Emphy-

sematous changes as part of lymphohematogenous dissemination can be of various nature. In acute miliary tuberculosis, the tubercles may contain small air bubbles in their necrotic centers, giving the lung a spongy appearance. Pagel gives a beautiful illustration of such a rare case (Fig. 1), which is classified here as intrafocal emphysema.

tuberculosis" there is extensive disseminated fibrosis, and marked reduction in elastic tissue (Fig. 8, *A* and *B*).

Endobronchial tuberculosis cannot be ignored as a contributing factor in the development of emphysema as part of hematogenous pulmonary tuberculosis. In his classical description Pagel has demonstrated that such tuberculous endobron-

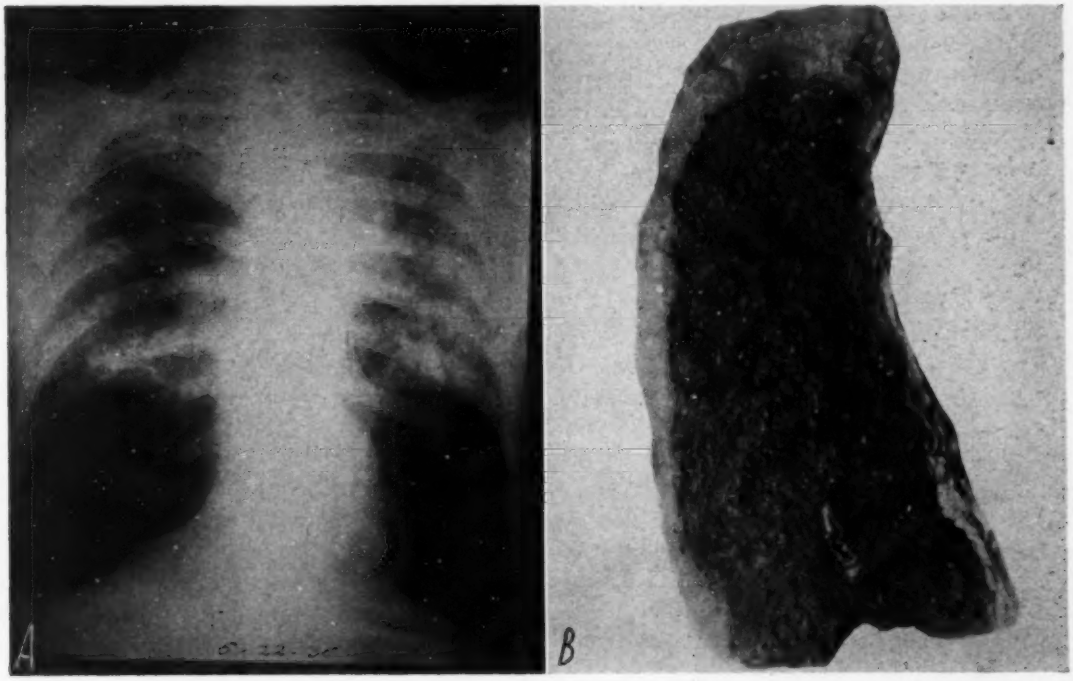


Fig. 8. *A*, fibrotic lesions in both lungs. Emphysema with bleb formation in lower thirds. *B*, emphysematous form of chronic hematogeneous pulmonary tuberculosis. Numerous small blebs and bullae; extensive fibrosis.

An outstanding feature in many cases of chronic hematogenous pulmonary tuberculosis is the characteristic form of the complicating emphysema (Pagel[7]). It is a known fact that in such forms of pulmonary tuberculosis, the individual lesions are of a productive nature, and that dyspnea plays an important part in their symptomatology. If we accept the theory that in hematogenous tuberculosis the original pulmonary lesions are formed in the interstitial tissue, then these is no difficulty in explaining the symmetrical localization of the emphysematous areas. In such "emphysema-

chitis is frequently part of hematogenous tuberculosis.

In more acute cases of generalization in which the individual lesions are of a caseous pneumonic nature, there is a distinct tendency to calcification. Again the secondary emphysema becomes of pathological and clinical importance, much more so than in isolated pulmonary tuberculosis. It is in such cases that we find extensive circulatory disturbances, consisting of atheromatosis and sclerosis of pulmonary vessels, and acute and chronic dilatation of the right heart.

Emphysematous bullae and blebs are frequently found in widespread chronic hematogenous tuberculosis. Many of the apical blebs are caused by scar tissue which in turn resulted from abortive hematogenous spreads ("fibrosa densa," Simon foci).

(3) *Chronic Isolated Pulmonary Tuberculosis.* Emphysema in the early exudative stages of chronic pulmonary tuberculosis is of minor importance. Only as a contributing factor in the formation of rapidly developing cavities does emphysema gain in significance. These are probably intrafocal air collections, with round thin-walled cavities, which, if cut off from a constant air supply, may shrink rapidly and close spontaneously.

The more chronic the tuberculosis becomes, and the more fibrosis develops, the more significant becomes the complicating emphysema. It was mainly in cases in which there was an extensive loss of normal lung tissue that the expression "compensatory" emphysema was employed. One of the outstanding symptoms in the vast majority of cases of chronic pulmonary tuberculosis is the copious sputum which occupies one or more parts of the bronchial tree at all times. We therefore believe that at least part of the emphysematous changes should be attributed to bronchial obstruction, and not merely to a purely compensatory mechanism. Even in cases in which both upper lobes are replaced by huge cavities, emphysema does not necessarily develop in the remaining normal lower lobes. Hypertrophic emphysema of a lobe or even of an entire lung does not develop very rapidly. It may take several years before the characteristic features of so-called compensatory emphysema become roentgenologically manifest: decreased lung markings, stretching of bronchial and vascular structures, widening of intercostal spaces, and a depression of the diaphragm (Fig. 9 and 10). The autopsy in such cases does not only reveal a distention of alveolar structure, but also an almost complete absence of bronchioli. On the other hand, an often considerable dilatation of larger bronchi can be found.

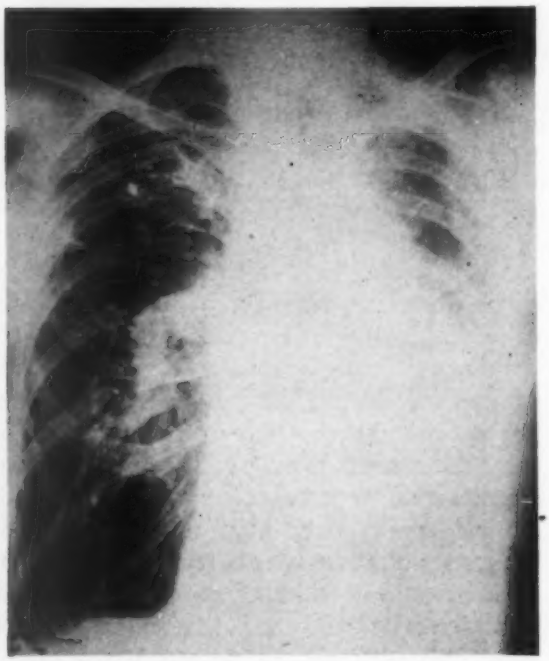


Fig. 9. Fibrosis of the left lung. Fibrocalcific lesions on the right with extensive emphysematous changes.

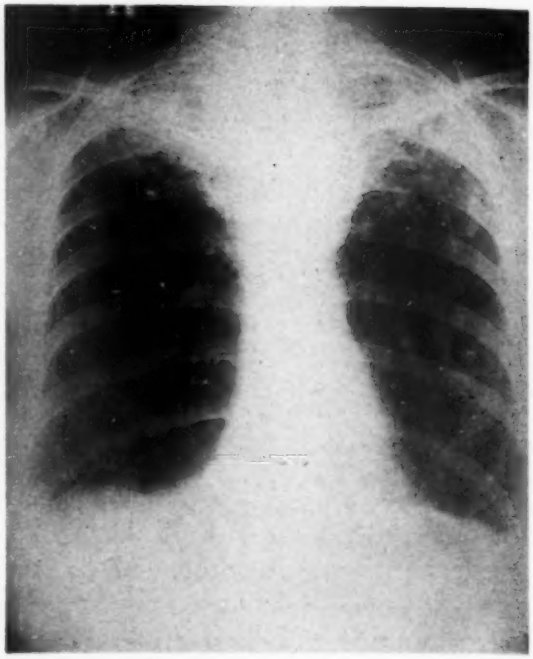
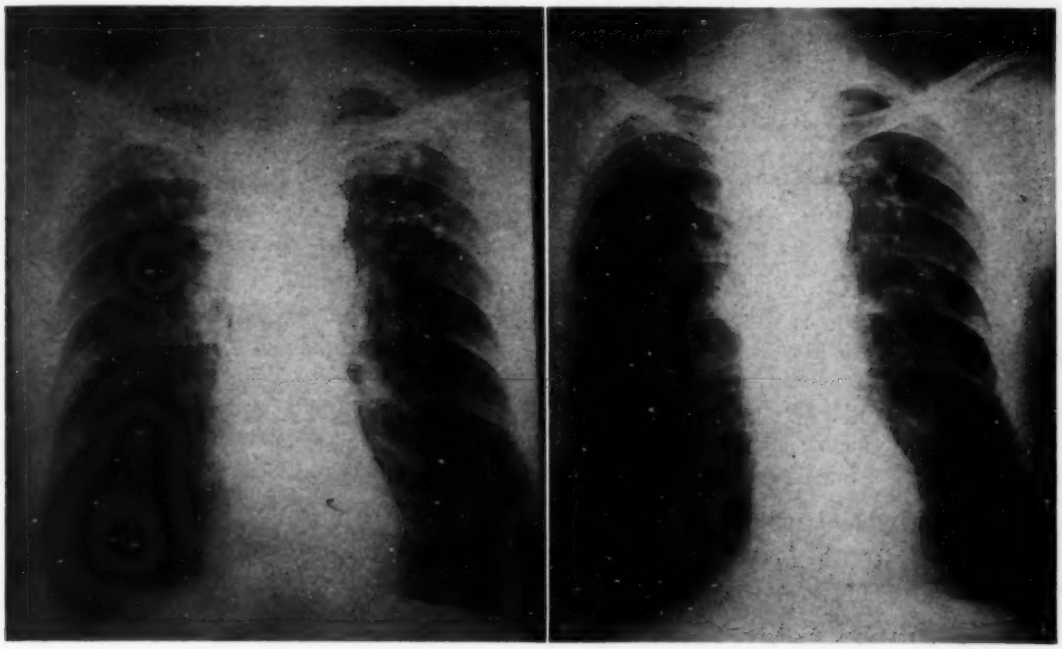


Fig. 10. Fibrosis of both upper lobes. Stretching of bronchovascular structures. Emphysema of lower portions of lung.

Although all forms of hypertrophic emphysema are to be found in chronic pulmonary tuberculosis, perifocal emphysema is most frequent. Bullae and blebs are features of clinically arrested lesions, and it is in such cases that spontaneous pneumothorax occurs most frequently (Fig. 11, *A* and *B*).



A *B*

Fig. 11. *A*, emphysema in fibrocalcific tuberculosis. Blebs in lower lobes. *B*, simultaneous spontaneous bilateral pneumothorax. The bleb in the right lower lobe did not collapse.

Emphysema and Collapse Treatment

The clinical and pathological significance of emphysematous changes during and after collapse treatment should not be overemphasized. It is a well known fact that after the artificial collapse of a diseased lung the pulmonary function not only does not decrease but that there is actually an improvement in the breathing capacity of many patients.

There can be no doubt, however, that during pneumothorax treatment as well as after thoracoplasty, hypertrophic emphysema does occur in many cases. After part of a lung has become fibrotic following thoracoplasty, the non-collapsed tissue may show emphysematous changes. This emphysema is not always due to a purely compensatory process. There is frequently a displacement and torsion of mediastinal structures, and a partial fixation of the bony thorax. The resulting changes of the bronchial tree contribute to the formation of hypertrophic emphysema.

During pneumothorax treatment similar changes may take place, and bleb-like bulgings in the collapsed lung can be observed in many cases (Fig. 12). Following re-expansion of the lung such emphysematous areas will frequently disappear. In pneumothorax an overextended lobe or part of it can practically always be explained on a bronchogenic basis. Massive collapse (atelectasis) which sometimes follows emphysema in a pneumothorax lung points in the direction of bronchial narrowing and subsequent occlusion of the lumen.

In all those cases in which the contralateral lung offers roentgenological and pathological evidence of emphysema it has been found that there is almost without excep-

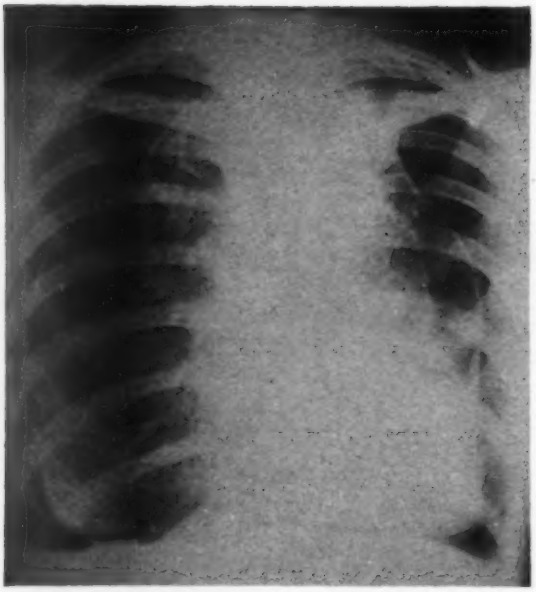


Fig. 12. Bilateral artificial pneumothorax, with bleb-like emphysema. Thickening of visceral pleura. Repeated spontaneous pneumothorax, right.

tion, a marked shrinkage of the collapsed lung with shifting of the mediastinum which is not pushed but pulled towards the shrunken lung. Even if the contralateral lung was free of tuberculous lesions, localized emphysema may develop on the basis of bronchial changes.

DISCUSSION

Up to the present time emphysematous changes in pulmonary tuberculosis have been considered part of a purely compensatory process, except for those cases in which bronchial obstruction could be clearly demonstrated. There is no doubt that in long standing tuberculous processes with considerable reduction of respiratory surface, the uninvolved parts of the lung will undergo certain changes which ultimately will lead to emphysema.

The pathogenesis of emphysema is still a subject of discussion now, as much as it was at the time when Laennec[4] first introduced the obstruction theory of pulmonary emphysema. Since then many theories have been promulgated, most of which had to be abandoned because of too little or no proof.

In discussing the pathogenesis of any form of pulmonary emphysema, it is necessary to differentiate between hypertrophic and atrophic emphysema. The atrophic form which occurs as part of a general atrophy of the body will not be discussed in detail. Its clinical and pathological features are well known, but as far as its pathogenesis is concerned there is a marked difference of opinion. The theory of Trippier that in the early stages of emphysema the elastic fibres are hypertrophied is opposed especially by Tendeloo[10] who does not find definite changes in the elastic tissue which can be made responsible for early emphysematous changes. Letulle,[5] on the other hand, brings definite proof that in the later stages of emphysema the alveolar walls separate from the basal membranes, and that blood vessels and elastic fibers in the septa become atrophic. The original opinion of Virchow[12] that primary decrease of elasticity through atrophy leads to emphysema is opposed by Thannhauser[11] who believes that loss of elasticity is the result and not the cause of the disease. That fixation and deformities of the bony structures of the thorax frequently lead to emphysema was already recognized by Freund[2] in 1859.

True atrophic emphysema is rarely seen in cases of pulmonary tuberculosis, probably because the vast majority of the cases belong in the lower age groups. For a long time the possibility of their simultaneous occurrence was very much disputed, but there is no doubt that in the aged atrophic emphysema and tuberculosis may coincide. The tuberculous lesions in such cases are usually of an exudative type.

Hypertrophic emphysema has been attributed to two major causes: bronchial obstruction, and hyperventilation of the lungs without obstructive changes. It has not been definitely proved that musicians, glassblowers, and high altitude workers develop true hypertrophic emphysema. The overventilation of the lung in such cases is of a temporary nature, and does not necessarily lead to permanent anatomical changes. Many cases of functional emphysema as described by Mayer and Rappaport[6] probably fall into this group. En-

largement of the lung, especially when of a temporary nature is not synonymous with hypertrophic emphysema.

It is well known that after thoracoplasty, lobectomy, and pneumonectomy the remaining parts of the lung become enlarged. It is not at all certain that such a hypertrophy must lead to hypertrophic emphysema. There is, however, the possibility that in such lungs atrophic changes will occur much earlier in life than usual. We may be able to use the well known experiments in dogs as proof of this fact. Within a year after pneumonectomy no clinical or pathological evidence of emphysema could be found (Rienhoff, Reichert and Heuer,[9] Bremer[1]); however, several years later emphysematous changes were detectable on autopsy (Paine).[8] We believe that pure compensation cannot be the sole cause of hypertrophic emphysema; in an otherwise normal lung the abundance of elastic and muscular tissue would not permit the permanent and progressive dilatation of alveoli, and to stretching and rupture of interalveolar septa.

There are two conditions which are almost always found in hypertrophic emphysema: (1) bronchial and bronchiolar obstruction, and (2) vascular changes in the lung.

(1) It is well known that under certain pathologic conditions acute dilatation of the lung can occur; however, in many cases such changes are reversible, and do not lead to hypertrophic emphysema. In acute respiratory infection such as whooping cough, diphtheria, and edema of the larynx, there is a temporary hypertrophy of the lung, but after the acute disease has passed, the lung shows a normal roentgen appearance. The changes have been caused by temporary bronchial obstruction. The classical example of acute emphysema due to bronchial obstruction is seen after drowning. Air and water are aspirated simultaneously and the lung may reach tremendous proportions (volumen pulmonum auctum). Only if the obstructing water can be removed from the air passages, can respiration be resumed.

Obstruction explains the development of emphysema not only in such acute diseases, but also in diseases of a chronic nature. The best example is chronic bronchial asthma, during the course of which the bronchial lumina are narrowed by spasm, swelling of the mucosa, and by exudate. It is therefore not surprising that emphysema develops in almost all patients with long standing asthma (Kountz and Alexander).[3]

In all forms of pulmonary tuberculosis, exudate in the bronchial tree occurs quite frequently, and it can be assumed that in the majority of cases localized emphysema is due to obstruction (localized drowning). In an attempt to analyze the role of bronchi and bronchioli we carefully investigated the bronchial tree in 10 cases of chronic pulmonary tuberculosis. In the vicinity of cavities and of exudative lesions we could always find one or more bronchi or bronchioli which showed tuberculous involvement of the mucosa, leading to narrowing or to occlusion of their lumina. After complete obliteration of the lumen, atelectasis will develop, because the air in the alveoli distal to the obliteration is absorbed and no fresh air can enter. We know now that such a mechanism is a prerequisite for the closure of cavities. However, the closure of cavities and the healing of exudative lesions by fibrosis produce pressure or torsion, involving the bronchial structures in the surrounding areas, leading to localized emphysematous changes. Microscopic emphysema to large blebs can be explained as the result of such a mechanism.

While the lung with senile atrophic emphysema collapses after the pleural cavity is opened, the hypertrophic emphysematous lung does not retract. This difference in behavior can be used as definite proof that air can escape from the intrapulmonary air passages in atrophic emphysema where bronchial obstruction is of little or no importance; the involved portions of the lung in hypertrophic emphysema do not collapse because of the valvular mechanism in the regional bronchioles.

(2) While in atrophic emphysema ather-

omatous and sclerotic changes in pulmonary vessels are of primary importance, in hypertrophic emphysema they are the result and not the cause of emphysema.

(a) In hypertrophic emphysema pathological changes are usually found in capillaries but not in larger vessels as in atrophic emphysema. Along respiratory bronchioles the capillaries are stretched, their lumina are narrowed and often obliterated. In many emphysematous areas no capillaries are found at all, a fact which explains the anemic appearance of emphysematous lung tissue. Although the histological proof is a difficult one, we assume that not only are the pulmonary vessels involved, but also the bronchial arteries and veins. The few capillaries which are found in emphysematous tissue are thin walled, dilated, and sometimes congested with blood.

The result of such vascular changes are nutritional disturbances of the lung parenchyma which in turn create additional degenerative processes (atrophy, necrosis, fibrosis).

(b) Emphysema is also found in congestion of pulmonary vessels as part of chronic heart disease. If the pulmonary circulation is impaired, the blood vessels are engorged, and exudate or transudate is found in the air spaces. In the extreme case of pulmonary edema, emphysema is part of the pathological findings.

(c) The behavior of the lymph vessels has been quoted in explaining healing processes in tuberculous lungs, especially as the result of collapse treatment. It is believed that congestion of lymph vessels stimulates fibrosis, and at the same time causes degeneration of elastic fibers. We know that elastic fibers are well preserved in caseous foci, while in fibrotic areas they are almost entirely absent. Although there is no direct proof, we believe that changes of the intrapulmonary lymph vessels play a part in the development of pulmonary emphysema.

SUMMARY AND CONCLUSIONS

1. An analysis of emphysema in pulmonary tuberculosis leads to the conclusion that in only a small minority of the cases can the changes be explained on a purely compensatory basis.

2. Localized emphysema, whether intrafocal or perifocal, as well as bullae and blebs, is due to bronchial changes.

3. Obstruction of bronchi and bronchioles is caused by exudate, necrotic material, endobronchial tuberculous lesions, compression, torsion, and stretching.

4. In hypertrophic emphysema bronchial changes are of primary importance, while in atrophic emphysema vascular changes are of greater significance.

5. Emphysema occurs during all stages of pulmonary tuberculosis. It is of characteristic appearance in many cases of hematogenous tuberculosis.

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LOEFFLER'S SYNDROME

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SCATTERED case reports of transitory lung infiltrations accompanied by eosinophilia have appeared in the literature from time to time under the designation of Loeffler's syndrome[4] and tropical eosinophilia.[1] The etiology of this condition is not definitely known, although some observers have felt it to be an allergic response of the pulmonary tissues to a wide variety of allergens. It has been found associated with pulmonary tuberculosis; infestation with *Ascaris lumbricoides*, *Necator americanus* and *Endamoeba histolytica;* pollen hypersensitivity; asthma; chronic brucellosis[3,5] and strongyloidiasis.[2] The benignity of the disease has prevented pathological observation. It has been postulated that in the course of certain infestations characterized by larvae, migrating through the lung tissues, the pulmonary changes may be due to hemorrhage from mechanical rupture of the alveolar walls or a cellular reaction to which infection may or may not be added.[2]

The symptoms are generally mild, usually consisting of cough with or without chest pain, and moderate amounts of sputum. Fever is as a rule absent. Roentgen examination of the chest usually shows a well defined area of infiltration, most often, but not necessarily, in the lower lung fields. The infiltration may be single or multiple, unilateral or bilateral, and is often completely resolved in one week's time. It may on occasion persist for four weeks or more. In some instances new areas of infiltration have appeared after the older areas have resolved. Pleural effusion has been reported. The pertinent laboratory findings are an eosinophilia varying from 10 to 80 per cent and an elevation of the erythrocyte sedimentation rate. The prognosis is uniformly good and the treatment that of the underlying condition.

CASE REPORT

H. H., a white soldier, aged twenty-three, had the onset of his present illness on September 3, 1945, with a "cold" which persisted to admission on September 15. There was moderate nasal congestion, cough and the expectoration of yellow phlegm. He had had frequent night sweats but no chest pain or loss of weight. No chills or fever had been noted. In the past year, he had not felt completely well and complained mainly of weakness and intermittent headaches. The past history revealed pneumonia in December, 1942, and recurrence in January, 1943, three days after discharge from the hospital. His first attack of malaria occurred four weeks before the present admission. There was no history of allergic manifestations either in the patient or in his immediate family.

Physical examination on admission revealed a thin, pale soldier. There was capillary injection of the sclera and posterior pharynx. The remainder of the examination was not unusual.

Laboratory findings: September 17.

Malaria smear was negative. Complete urinalysis was normal. Hemoglobin 95 per cent (Sahli). Erythrocyte sedimentation rate 34 mm. per hour (Wintrobe). Twenty-four hour sputum examination—three specimens were negative for acid-fast bacilli. Three stool examinations were negative for ova and parasites. A fourth examination on September 27 was positive for cysts of *Endamoeba histolytica*. Proctoscopic examination showed a normal rectal wall.

	Blood Counts			
Date	Total Leukocyte Count	Neutrophils	Eosinophils	Lymphocytes
		per cent	*per cent*	*per cent*
Sept. 17	7,100	61	14	14
Sept. 20	8,200	46	6	46
Sept. 24	10,600	77	9	13
Sept. 29	5,900	46	10	46

A roentgenogram of the chest taken on September 15 (Fig. 1) shows a well defined, ovoid

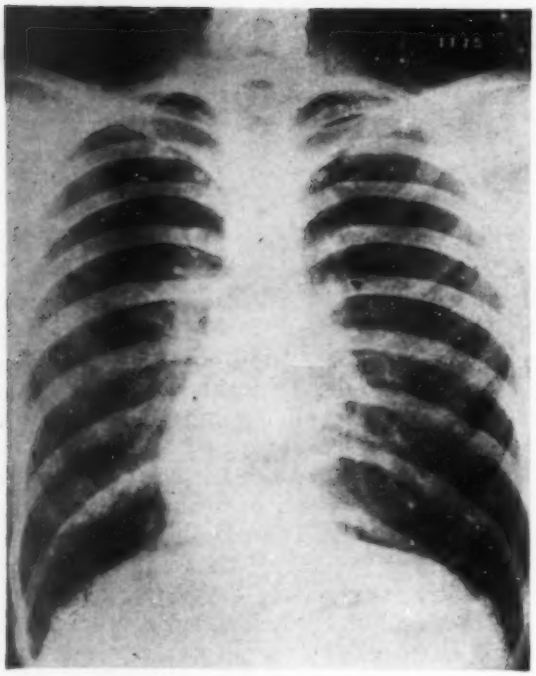

Fig. 1

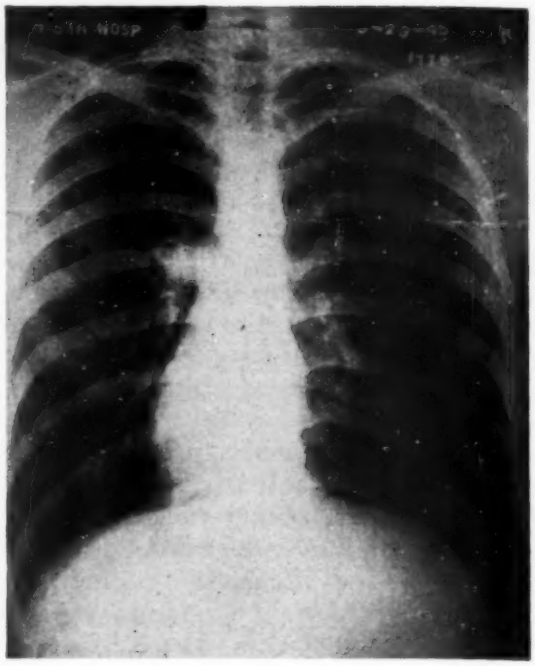

Fig. 2

area of increased density in the left lower lung field about the size of a silver dollar. There is an accentuation of the bronchovascular markings to the left lower lobe. A roentgenogram of the chest taken on September 24 (Fig. 2) shows that complete resolution of the infiltration has taken place.

Course. The patient was afebrile throughout. There was moderate cough and expectoration for the first few hospital days; thereafter he was asymptomatic. Carbarsone therapy was instituted on September 28 for amebiasis. Thereafter there was further subjective improvement.

DISCUSSION

A case of lung infiltration associated with eosinophilia and asymptomatic chronic amebiasis has been presented. At no time were the pulmonary symptoms more than minimal. The benign course, the rapid resolution of the lesion, and the blood findings fit in with the diagnosis of Loeffler's syndrome. It is suggested that many similar cases may be found in association with infestations if more emphasis is placed on roentgen examinations of the chest, especially in the presence of cough, expectoration and chest pain.

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Vol. 58, No. 1

ROENTGENOLOGIC CHARACTERISTICS OF DIAPHRAGMATIC HERNIA*†

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I. INTRODUCTION

ALTHOUGH diaphragmatic hernia has been known in the literature for several hundred years, the roentgenologic aspects of this condition are of fairly recent inception. The development of our present ideas about the roentgenographic and roentgenoscopic diagnosis of diaphragmatic hernia does not appear to be the work of one man or of a few men, but rather the composite effort of a great many men. In the period from 1910 to 1920 isolated case reports of diaphragmatic hernia diagnosed by roentgenologic means began to appear. Between 1913 and 1935 many significant articles appeared in the roentgenologic literature.[1,2,6,9–11,19,30,31,33,40,42,46,49,56,62] Roentgenologists, by this time, had seen enough cases to form a small series and with the publishing of their experiences and observations, a fund of information concerning the roentgenoscopic and roentgenographic diagnosis of diaphragmatic hernia was established. The contributions of later authors further added to the knowledge of diaphragmatic hernia.[5,13–16,22–24,26,27,37,39,43,45] These and many other noteworthy additions to the knowledge of diaphragmatic hernia have functioned to increase further the accuracy and usefulness of attempts to diagnose correctly all variations of this condition.

II. EMBRYOLOGY

Some understanding of the fundamentals of the embryology of the diaphragm is a necessary prerequisite for accurate diagnosis.[14,24,33,54]

There are two important factors in the embryology of the diaphragm. They are (1) the source of the several components of the diaphragm and (2) the points in the diaphragm where these components fuse. The point of fusion is a place of weakness and is therefore a frequent site of diaphragmatic hernia.

The diaphragm may be considered as consisting of a membranous component and a muscular component. The membranous diaphragm is derived from a number of separate elements. First in importance among these is:

1. *The septum transversum.* This is made up of mesoderm and serves as an early but incomplete diaphragm. From this septum transversum or ventral mesentery are derived the membranous elements of the diaphragm which are ventral, or anterior, and central, including the portion of the diaphragm which is below the heart. The septum transversum by means of lateral segments also gives rise to the costal portion of the membranous diaphragm on each side.

2. The posterior and medial portion of the membranous diaphragm is derived from the *dorsal mesentery.* Embryologically this is the last portion of the diaphragm to form.

3. The posterior lateral elements of the diaphragm are derived from the paired *pleuroperitoneal membranes.* These membranes fuse laterally with the costal portion of the transverse septum and medially with the portions derived from the dorsal mesentery to complete the partition between the pleural and the peritoneal cavity.

4. The *thoracic wall* provides a small part

* Read at the Forty-seventh Annual Meeting, American Roentgen Ray Society, Cincinnati, Ohio, Sept. 17–20, 1946.

† Abridgment of thesis submitted by Dr. Hodgson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Roentgenology.

of the membranous diaphragm in the costal region bilaterally.

These four elements are therefore the source of the membranous diaphragm. Defects occurring in their development will result in defects in the diaphragm.

The muscular elements of the diaphragm are derived from two sources. Some invade the diaphragm at the level of the fourth cervical segment in 9 mm. embryos. There are also some muscle derivatives from the lateral body walls which form a component of the muscular elements of the diaphragm.

Therefore there are really four general groups into which the hernias through the diaphragm may be placed according to their embryologic development:

1. The foramen of Bochdalek, which is posterior and which is covered by the pleuroperitoneal membrane. It is a point of fusion and is a potential spot for diaphragmatic hernia.

2. The foramina of Morgagni, which are anterior on each side of the sternum and are a second potential weak spot in the diaphragm.

3. The esophageal hiatus in the muscle of the diaphragm on the left side. Failure of complete development of this hiatus may permit the herniation of the stomach through it.

4. Deficiencies of the other elements of the diaphragm. The embryologic development of any segment of the diaphragm may be stopped at any time. Variations of this process may result in complete absence of half of the diaphragm or small openings anywhere in the substance of the diaphragm.

III. ANATOMY

For the purposes of discussion we shall divide the diaphragm into three elements according to their anatomic origin.

A. The *sternal portion* arises from the posterior surface of the xiphoid process and consists of a pair of short, narrow muscular slips that pass backward and upward to be inserted into the central tendon.

B. The *costal portion* of the diaphragm arises from the inner surfaces of the lower six costal cartilages and inserts into the anterolateral borders of the central tendon or aponeurosis.

C. The *vertebral portion* of the diaphragm arises from the lateral and ventral sides of the bodies of the first three lumbar vertebrae. This portion of the diaphragm will be considered as two distinct elements for the purpose of simplification. These are, (1) the crura and (2) the arcuate ligaments.

1. The *crura* are a pair of musculotendinous elements arising from the first, second and third lumbar vertebrae on the right and from the first and second lumbar vertebrae on the left. The left margin of the right crus is directed obliquely upward and to the left in front of the aorta. It splits as it approaches the central tendon to form an elliptical opening for the esophagus. Thus the esophageal opening is surrounded by a sphincter-like arrangement of this muscle. The left crus is more variable in size and attachments than the right crus and is usually smaller.

2. There are two *arcuate ligaments*—medial and lateral. The *medial* arcuate ligament runs laterally and posteriorly from the aorta and gives off fibers which join the right crus as it splits to encircle the esophagus.

The *lateral* arcuate ligament arises from the transverse process of the first or second lumbar vertebra and arches across the upper part of the quadratus lumborum to be attached to the eleventh or twelfth rib.

The superior border of these ligaments gives rise to muscular fibers which make up a part of the posterior segment of the diaphragm and which are inserted into the central tendon.

The opening in the diaphragm for the esophagus is of great interest to the roentgenologist. Harrington[21] in his excellent monograph on this subject has emphasized the importance of the anatomy of the esophageal opening in the diaphragm.

Harrington pointed out that the diaphragmatico-esophageal membrane and the loose attachment of the peritoneum at the

cardia are extremely important in the development of hiatus hernias. Harrington further stated that the hiatus hernias of elderly people which are accompanied by insufficiency of the hiatus are probably due in part to atrophy of this protective elastic membrane especially where, to begin with, there may be an abnormally large hiatus. Another factor which might also be considered with the atrophy of age is the general tendency toward obesity of people in this group, which may have some effect on the development of diaphragmatic hernia of the hiatal variety.

IV. CLASSIFICATION

Many classifications have been devised for diaphragmatic hernia. In fact their number is almost equal to the list of articles on the subject. The ideal classification would be that which is very simple and yet contains a maximum of information.

Harrington[24] has proposed what seems to us to be the most complete classification of these lesions. It combines the various elements in such a way as to be most informative to the surgeon, the clinician and the roentgenologist. We have added eventration, although it is not a hernia, since we wish to discuss the differential diagnosis of this condition from hernia.

A. Diaphragmatic hernia
  I. Nontraumatic lesions
    a. Congenital
      1. Pleuroperitoneal (foramen of Bochdalek)
      2. Esophageal hiatus (congenital type)
        (a) Para-esophageal
        (b) Esophageal hiatal
      3. Short esophagus
        (a) Congenital short esophagus
      4. Anterior substernal (foramen of Morgagni-Larrey's spaces)
      5. Gaps in or partial absence of the diaphragm (posterior portion of the diaphragm)
      6. Complete absence of hemidiaphragm
    b. Acquired
      1. Esophageal hiatus
        (a) Pulsion type
          (1) Similar to para-esophageal
          (2) Similar to esophageal hiatal
      2. Short esophagus
        (a) (Not congenital) ulceration and cicatricial contraction which draws the stomach above the diaphragm.
      3. Through regions of fusion of the anlage of the diaphragm
      4. At sites named in the congenital type
  II. Traumatic
    a. Indirect injury
      1. Anywhere in the diaphragm
      2. Points of embryologic fusion
      3. Dome and posterior half of the diaphragm
    b. Direct injury
      1. Any point in the diaphragm
    c. Result of inflammatory necrosis
      1. Subdiaphragmatic abscess or drainage tubes
      2. Usually posterior portion of the diaphragm
B. Eventration

In this paper we shall not follow this classification in exact order. For the purposes of clarity all esophageal hiatal hernias will be discussed together.

V. INCIDENCE

Ideas concerning the incidence of diaphragmatic hernia have changed with the advent of their more frequent diagnosis. This is especially true of esophageal hiatal hernias, which were formerly thought to be quite rare.[16]

Harrington[24] reported the incidence of diaphragmatic hernia based on 250 cases in which operation had been done between 1926 and 1940: esophageal hiatal hernia, 198; pleuroperitoneal hiatal hernia, 4; congenital absence of portion of left side of the diaphragm, 4; foramen of Morgagni hernia, 4; traumatic herniation through dome, 40. Thus he concluded that esophageal hiatal hernia treated surgically was about four times as common as all other types of herniation combined.

Harrington and Kirklin[27] reported that at the Mayo Clinic between 1900 and 1925 thirty cases were recognized and 19 patients were operated on. From 1925 to 1937, 211 cases were recognized and 131 patients were operated on.

In a series of 5,269 necropsies on stillborn infants and infants up to one year of age,

from the Department of Pathology of the University of Minnesota, Haugen and Ehrenberg[29] found 38 diaphragmatic hernias or one hernia in 139 necropsies.

We found on examination of our records at the Mayo Clinic that diaphragmatic hernias of all types occur with a frequency of between 1 and 2 per cent of all gastrointestinal examinations.

VI. CLINICAL ASPECTS

Before the advent of roentgenology, the diagnosis of diaphragmatic hernia was extremely difficult and rarely made. A discussion of the complete nature of the clinical aspects of diaphragmatic hernia is outside the scope of this paper. However, the close relationship between certain of the symptoms and the roentgenoscopic diagnosis requires a brief consideration of some of the clinical features of diaphragmatic hernia. For more complete information regarding this aspect of diaphragmatic hernia the reader is referred to articles by Polley,[50] Giffin,[21] Harrington[24] and others.[27]

Some diaphragmatic hernias are symptomless. In others the symptoms are very slight. Variable symptomless periods are common and are probably due to temporary spontaneous reduction of the hernia.

In the traumatic type of diaphragmatic hernia a history of injury is of importance. Diaphragmatic hernias may not develop coincident with the injury but may present themselves at a later date. Carman and Fineman[10] suggested that this type of diaphragmatic hernia may not develop until months or years after the injury.

Harrington and Kirklin[27] have stated that the symptoms depend on three factors. (1) the mechanical interference with herniated viscera, (2) interference with function of the diaphragm and (3) the amount of increased pressure within the thorax.

The most frequently encountered symptom in cases of diaphragmatic hernia is substernal pain.[50,53] Other symptoms described are nausea and vomiting, bloating and belching, heartburn and disphagia, and dyspnea.

The physical signs of diaphragmatic hernia are highly variable. The roentgenogram of the thorax is of much more definitive value than physical signs.

Bleeding occurs in a certain number of cases of diaphragmatic hernia.[7,20,50,58] It is due to the erosion and ulceration of gastric mucous membrane within the hernia. The erosion and ulceration is on the basis of a chronic or recurrent venous congestion. A certain amount of pressure is exerted by the margins of the hernia on the vascular supply. This produces the venous congestion, which in turn is the precursor of a chronic inflammatory state of the gastric mucous membrane.

VII. ESOPHAGEAL HIATAL HERNIA

Prior to the appearance of articles on hiatal hernia in the decade 1920 to 1930 it had been felt that esophageal hiatal hernia was an extremely rare lesion.[16] Subsequent investigation has shown that esophageal hiatal hernia is the most common type of diaphragmatic hernia. In a review of the cases in which diaphragmatic hernia was diagnosed roentgenologically for the year 1944 at the Mayo Clinic, we found that diaphragmatic hernia at the esophageal hiatus represented more than 98 per cent of all the cases of diaphragmatic hernia. All diaphragmatic hernias occur with a frequency of between 1 and 2 per cent of all gastrointestinal examinations.

Jackson and Jackson[34] stated that hiatal hernia is a rather common condition in their records. Åkerlund[2] in 1926 showed that esophageal hiatal hernia is six to seven times more frequent than the other varieties. In 1940 Harrington[24] reported 250 cases in which treatment was surgical, of which 187 were of the esophageal hiatal type. In addition there were 11 cases of the short esophagus type. Of our 306 cases in which esophageal hiatal hernia was diagnosed roentgenologically in 1944, 31 were of the short esophagus type and an additional 51 cases presented what appeared to be a shortened esophagus. There has been much confusion over the use of the term

"short esophagus." In order that there may be no misunderstanding, we shall attempt to clarify our interpretation of these terms now.

There are a number of types of hernia present at the esophageal hiatus. For the purposes of simplification we shall discuss the hiatal hernias as a group, including those lesions which are not true hernias and also those lesions which may be acquired, whose straight short esophagus ended at the third costal cartilage and in whom there was no evidence that the stomach had herniated through the diaphragm. In cases of congenitally short esophagus with thoracic stomach the stomach has not herniated through the esophageal hiatus of the diaphragm, since it never was below the diaphragm at any time. The thoracic position of the stomach is due to the failure of the

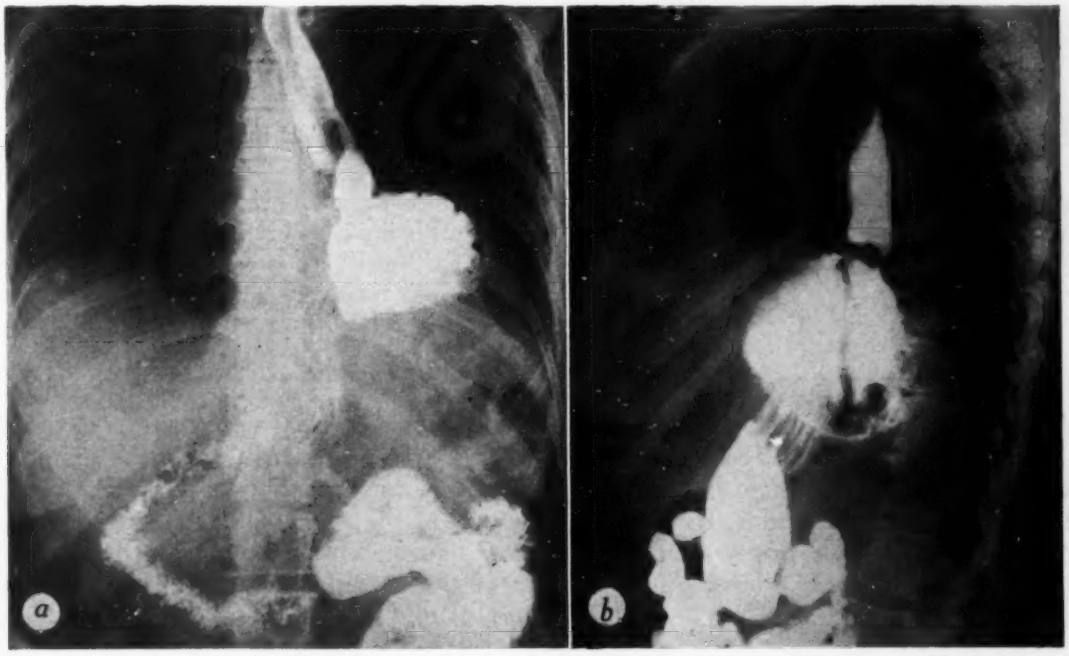

FIG. 1. Congenitally short esophagus in the case of a forty-four year old woman. *a.* Esophageal hiatal hernia containing five-sixths of the stomach, a loop of transverse colon and a portion of the spleen. The esophageal hiatus was extremely large (12 cm.) and at operation the surgeon felt that this was probably a true congenitally short esophagus. The roentgenogram shows a large part of the stomach above the diaphragm. *b.* Lateral view of the thorax.

as well as congenital. An outline of these lesions is as follows: (1) congenitally short esophagus with thoracic stomach, (2) hiatal esophageal hernia with shortened esophagus, (3) esophageal hiatal hernia and (4) para-esophageal hernia through the esophageal hiatus.

Congenitally Short Esophagus with Thoracic Stomach. This is a very rare lesion. Bailey[3] first proposed the term describing this type of lesion after postmortem examination of a seventy-seven year old man stomach to migrate caudad, to failure of the esophagus to maintain its longitudinal growth or, according to Jackson and Jackson,[34] to a congenitally large esophageal hiatus (Fig. 1).

The term "thoracic stomach" should be used only in conjunction with congenitally short esophagus. A survey of the literature reveals much confusion regarding this term and numerous articles have been published on conditions which are merely various types of diaphragmatic hernia masquerad-

FIG. 2. Esophageal hiatal hernia in a fifty-four year old woman with slight redundancy of the lower part of the esophagus.

ing under the name of "thoracic stomach."

Esophageal Hiatal Hernia with Shortened Esophagus. This represents 26 per cent of all esophageal hiatal hernias. By using the word "shortened" we imply that at one time the esophagus was longer but that it has now become shortened. Frequently what appears to be a short esophagus in the roentgenoscopic and roentgenographic examination of the upper part of the gastrointestinal system will prove to be capable of a considerable amount of stretching by the surgeon at operation. When diaphragmatic hernia occurs, a certain amount of redundancy of the lower part of the esophagus is present. It is possible that the normal muscle tone of the longitudinal muscle fibers of the esophagus adjusts itself to a state of contraction of these fibers which produces the apparent shortening of the esophagus. It is impossible to determine from roentgenoscopic and roentgenographic examination alone whether the apparently shortened esophagus is capable of being stretched or not. We feel that this shortening should be mentioned in the report of the disphragmatic hernia, however, since it may provide valuable information to the surgeon attempting repair.

On the other hand, in some of these cases the shortened esophagus may prove to be a congenitally short esophagus. Unfortunately the roentgenologist has no accurate method of determining which of these esophaguses are incapable of stretching and which are really congenitally short. Even knowing how infrequently congenitally short esophagus occurs it is still impossible to determine accurately in the individual case whether the esophagus is *short* or *shortened.*

Esophageal Hiatal Hernia. This type of hernia at this site refers to those cases in which the esophagogastric junction is above the diaphragm and both the stomach and the lower end of the esophagus are contained in the hernia (Fig. 2). This is the most common type of hernia encountered at the esophageal hiatus and represents 66.5 per cent of the group of esophageal hiatal hernias examined roentgenologically at the Mayo Clinic in 1944. In this group there is usually slight to marked redundancy of the lower part of the esophagus as distinguished from the shortened esophagus type. The only difference between this group and the group of esophageal hiatal hernias with shortened esophagus is the apparent length of the esophagus. They are otherwise the same.

Para-Esophageal Hernia through the Esophageal Hiatus. This is the type of hernia in which a portion of the stomach herniates through the esophageal hiatus of the diaphragm but the esophagogastric junction remains below the diaphragm and no esophagus is present within the hernia (Figs. 3 and 4). This group represents 7.5 per cent of all the esophageal hiatal diaphragmatic hernias examined roentgenologically at the Mayo Clinic in 1944. Any part of the stomach may be involved in this hernia. It is more frequently the cardia but we have encountered cases in which the midportion of the stomach and also the pyloric segment of the stomach were involved.

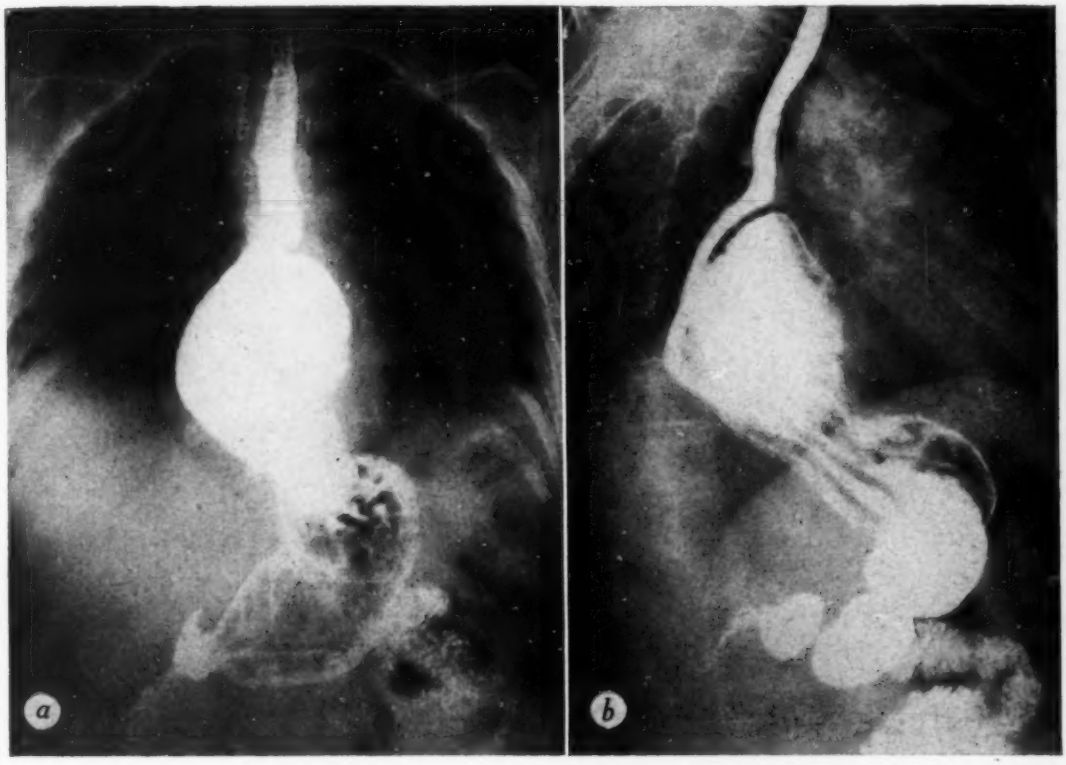

Fig. 3. Para-esophageal hernia at the esophageal hiatus in the case of a sixty-four year old woman. *a.* The cardiac half of the stomach has herniated through a defect in the posterior portion of the esophageal hiatus. *b.* Lateral roentgenogram which demonstrates the course of the esophagus with the esophagogastric junction below the diaphragm and also emphasizes the importance of the lateral view.

Inflammatory processes in the esophagus in which cicatricial changes develop with resultant narrowing and gradual shortening may produce hiatal hernias. These fibrosing changes with resultant shortening produce hiatal hernias by a gradual pulling up of the esophagus which causes the herniation of a small portion of the cardiac end of the stomach through the esophageal hiatus (Fig. 5). One example of this condition is scleroderma of the esophagus, which has been described by Olsen, O'Leary and Kirklin.[47] In this disease the mucosa is involved and inflammation supervenes fol-

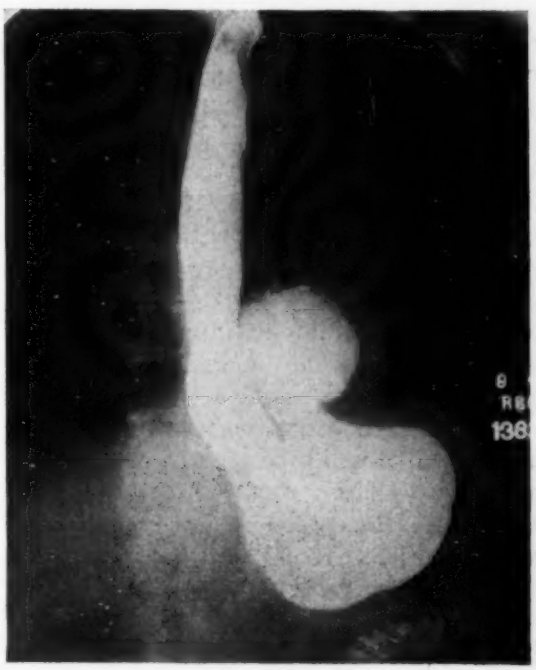

Fig. 4. Para-esophageal hernia at the esophageal hiatus in the case of a sixty-eight year old woman. The esophagogastric junction is below the diaphragm. The cardiac end of the stomach has herniated through the esophageal hiatus.

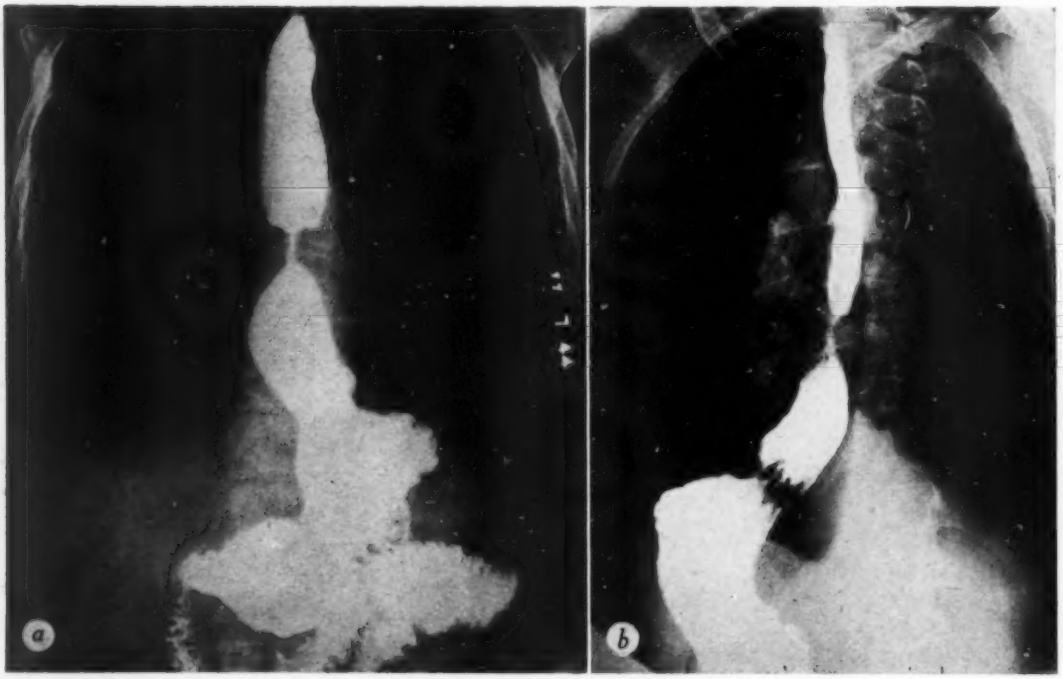

FIG. 5. Shortening of the esophagus with esophageal hiatal hernia in the case of a fifty-four year old man who had had trouble in swallowing for four to five years. Esophagoscopy revealed chronic esophagitis with stricture at the esophagogastric junction. It is probable that the chronic inflammatory process of the esophagus has caused shortening of the esophagus and subsequent development of the hernia. *a*. Notice the irregularity of the mucous membrane at the esophagogastric junction. *b*. Lateral view.

lowed by ulceration and scar tissue with cicatrix formation. Other inflammatory conditions involving the esophagus will also produce these changes. Examination of our records of esophageal hiatal hernia show that mediastinal tumors may cause displacement of the esophagus with resultant small esophageal hiatal hernias. Carcinoma of the esophagus with some inflammatory component frequently causes shortening with the production of small esophageal hiatal hernias (Fig. 6). Marked cardiac enlargement, if it causes esophageal displacement, may be an etiologic agent for small esophageal hiatal hernias. Ulcers of the esophagus from various causes and lesions which will produce upward traction on the esophagus must be considered as factors in the production of esophageal hiatal hernias.

We shall consider the congenital and acquired esophageal hiatal hernias together. They are definitely related and probably the greater percentage of this group are a combination of a congenital or developmental insufficiency with an acquired factor. Congenital defects at or near the esophageal hiatus sufficient to produce a hernia are probably not any more common than congenital defects in other parts of the diaphragm.

Harrington[27] routinely examined the esophageal hiatus in the course of operation on the abdomen in 1,000 consecutive cases at the Mayo Clinic. He found that in 55 per cent of these cases the esophageal hiatus closely approximated the lower end of the esophagus. In 35 per cent one finger could be inserted between the esophagus and the margins of the esophageal hiatus. In 8 per cent two fingers could be inserted and in 2 per cent two to three fingers could be placed between the esophagus and the edge of the esophageal opening.

Another important element in the development of the esophageal hiatal type of

hernia is the age of the patient. Harrington[24] has pointed out that the esophagogastric membrane is susceptible to atrophy, as is any other part of the body, and therefore atrophy of these fibers may result in a relative insufficiency of the esophageal hiatus.

Ritvo,[56] in a review of 60 cases, has listed the ages of the patients who had diaphragmatic hernia. His results are given in Table I.

Our figures for a group of 306 cases of esophageal hiatal hernia for the year 1944 at the Mayo Clinic are given in Table II.

There is slight variation. Our largest number of cases occurred between the ages of fifty and fifty-nine years, while Ritvo's greatest percentage fell in the forty-one to fifty year age group. It is interesting to note that in 92 per cent of our cases the esophageal hiatal hernia occurred after forty years of age.

Esophageal hiatal hernia occurs approximately twice as frequently in women as in men. This is in accord with Ritvo's conclusions. In his 60 cases, 41 patients were women and 19 were men. In our series of cases, 203 were women and 103 were men.

Table I

Age of Patients Who Had Diaphragmatic Hernia (Ritvo's Experience)

Age, Years	Cases	Per Cent
21–30	4	6.6
31–40	8	13.4
41–50	18	30.0
51–60	16	26.7
61–72	14	23.3

Table II

Age of Patients Who Had Esophageal Hiatal Hernia (Our Experience)

Age, Years	Cases	Per Cent
20–29	4	1.3
30–39	20	6.5
40–49	57	18.6
50–59	124	40.6
60–69	78	25.5
70–79	20	6.5
80–89	3	1.0

Fig. 6. Squamous cell epithelioma of the esophagus with esophageal hiatal hernia in the case of a fifty-nine year old man. There is an associated esophageal hiatal hernia. Gastric mucosa may be seen above the diaphragm in the roentgenogram. The esophageal hiatal hernia is probably secondary to changes brought on by the carcinoma of the esophagus.

Another important factor in the production of esophageal hiatal hernia is obesity. Harrington[26] has pointed out that he has long considered obsesity as a predisposing factor in the development of hiatal hernia. A search of the literature and an analysis of our cases reveals that this type of lesion occurs most frequently in obese middle-aged women.

Childbearing has been found to have a definite relationship to the development of esophageal hiatal hernia. Rigler and Eneboe[55] in 1935 concluded that increased intra-abdominal pressure, such as is pro-

FIG. 7. Large esophageal hiatal hernia with fluid level in the stomach seen in the roentgenogram of the thorax.

duced by pregnancy, especially when repeated, appears to be an important inciting cause for the production of esophageal hiatal hernias. In 1940 Evans and Bouslog[17] presented data on 4 pregnant women with severe "heartburn," all of whom had small hiatal hernias revealed by roentgenoscopic examination of the stomach.

There are a number of important points in the roentgenoscopic diagnosis of esophageal hiatal hernia. Each one will be discussed separately. If the hernia is large the diagnosis will not be difficult (Fig. 7). We shall concern ourselves with the diagnosis of small esophageal hiatal hernias.

First, the basic point of orientation in the diagnosis of esophageal hiatal hernia is the *esophagogastric junction*. The exact location of this basic point must be established in order to make an accurate diagnosis. If the esophagus is seen emptying into a large saccular portion of the stomach above the diaphragm the diagnosis is obvious. If, however, the hernia is small the exact location of the esophagogastric junction may not be so easily seen. The esophagogastric junction, in small esophageal hiatal hernias, must be differentiated from a peristaltic wave passing down the lower part of the esophagus. The point of differentiation is, of course, the constancy of the esophagogastric junction as opposed to the transitory nature of a peristaltic wave of the lower part of the esophagus. The location of the esophagogastric junction should be demonstrated to the satisfaction of the roentgenoscopist before roentgenograms of the hernia are made. Turning the patient in the various oblique positions is, of course, helpful. This is especially true when one is dealing with a para-esophageal hiatal type of hernia, in which the esophagogastric junction is below the diaphragm with a variable segment of stomach above the diaphragm.

The second point in the diagnosis of esophageal hiatal hernia is the retardation of the barium stream at the esophageal hiatus. This has been described by Morrison.[46] Morrison stated that normally the fluid column remains 2 to 3 inches (5 to 8 cm.) high in the lower part of the esophagus when barium is rapidly ingested. In nearly all cases of hernia the barium column remains 4 to 5 inches (10 to 13 cm.) high at the same rate of ingestion. Retardation of the barium stream should lead the roentgenoscopist to suspect the presence of hernia.

The third point in diagnosis of esophageal hiatal hernia is tortuosity of the lower part of the esophagus without dilatation. In reviewing our cases in which diaphragmatic hernia was diagnosed roentgenologically for the year 1944 we found that in more than a third of all esophageal hiatal hernias there was some degree of tortuosity of the esophagus without dilatation. If the esophageal hiatus is insufficient and hernia occurs there may be redundancy of the lower part of the esophagus which produces the tortuosity. Redundancy of the lower part of the esophagus with esophageal hiatal hernia is probably found early in the development of certain types of esophageal hiatal hernias. In close association with tortuosity of the lower part of the esoph-

agus is angulation of the lower part of the esophagus. This is especially true in the para-esophageal type of hiatal hernia where the herniated stomach causes displacement of the lower end of the esophagus.

Various techniques have been devised for better demonstration of the hernia while the patient is undergoing roentgenoscopic examination. The patient may be asked to take three swallows of barium mixture and to strain. This accomplishes two things: first, the deep breath produces a reduction of intrathoracic and intra-esophageal pressure and, second, straining raises the intra-abdominal pressure and aids in the demonstration of the hernia. This maneuver is simple and easily explained to the patient and occasionally produces the effect desired. Various other maneuvers, such as the Mueller test and the Valsalva test, have been described as producing the same effect. As a general rule these techniques have not proved to be of much value in the demonstration of esophageal hiatal hernias in our experience.

The position of the patient during the examination is also important. The best view of the lower part of the esophagus and the upper part of the stomach is obtained by turning the patient slightly to his left before the ingestion of the barium mixture. This will give the roentgenoscopist an unobstructed view of the lower part of the esophagus and the cardia of the stomach as the first swallow of the barium mixture reaches this region.

Our experience has led us to believe that changes which betray the presence of esophageal hiatal diaphragmatic hernia may almost always be seen with the patient in the upright position. In cases of doubt it is probably good policy to examine the patient in the horizontal position. Straining will sometimes make the borders of the hernia apparent with the patient in the horizontal position when the hernia is not very well seen in the upright position. Occasionally an esophageal hiatal hernia will not be seen in either position owing to spontaneous reduction of the hernia, when it has definitely been present on previous examinations.

Two roentgenograms of the patient are made. The patient lies recumbent on the table and a wooden support is placed under the right side in order to raise it approximately 15 degrees from the table top. A definite procedure is followed in obtaining the roentgenograms. A large paper cup containing a mixture of barium and water is given to the patient and he is instructed to drink half of the contents of the cup rapidly, then take a deep breath and strain with the abdominal muscles. At precisely this instant the roentgenogram is made. The average technical factors are as follows: 67 kv., 150 ma., target film distance, 38 inches; time, 0.3 second. The Potter-Bucky diaphragm is used.

The same procedure is used in obtaining the second roentgenogram except that the patient lies flat on his back. The patient is strapped to the table to aid in preventing motion and care should be taken to avoid motion as much as possible. It is more important to have the patient ingest a sufficient quantity of barium mixture than to be concerned about the straining of the patient. As a matter of fact the usefulness of straining in an attempt to produce the hernia may be questioned.

If the roentgenograms are at variance with the roentgenoscopic impression it is well to repeat the examination.

If the hernia is large enough it may be possible to demonstrate gastric mucosal folds in the roentgenogram of the herniated portion of the stomach. However, when the hernia is small and the mucosal folds of the stomach run parallel to those of the esophagus it becomes very difficult to use the appearance of the mucosal pattern of the stomach as a factor in making the diagnosis of esophageal hiatal hernia. Some confusion may arise between a cone-shaped dilatation of the lower end of the esophagus and a small esophageal hiatal hernia. If the location of the esophagogastric junction has been definitely determined roentgenoscopically, however, the interpretation of the

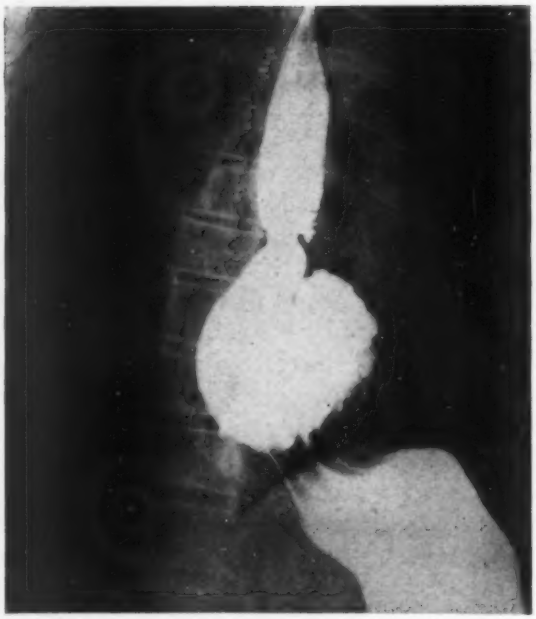

FIG. 8. Ulceration in an esophageal hiatal hernia in the case of a fifty-six year old man. A rather large portion of the stomach may be seen above the diaphragm. There is an ulcer at the esophagogastric junction. The esophagus is shortened. The presence of the ulcer was confirmed by esophagoscopy.

roentgenograms should not be difficult.

In reviewing our cases of esophageal hiatal hernia we divided the hernias into various groups depending on their size. In one group, which represented 73 per cent, we placed all those cases in which the hernia involved less than 3 inches (8 cm.) of stomach above the diaphragm. In a second group, which represented 20 per cent, we placed those in which the hernia involved 3 to 5 inches (8 to 13 cm.) of stomach. In the third group, which represented 7 per cent, more than 5 inches (13 cm.) of stomach was involved in the hernia.

Thus most of the esophageal hiatal hernias are small. However, we do feel that their early diagnosis is extremely important.

Ulcers of the stomach in cases of diaphragmatic hernia may be located in any region of the herniated stomach. They may be found at the esophagogastric junction (Fig. 8) or along the lesser curvature of the stomach. There is no specific location for their occurrence. They are not common in cases of esophageal hiatal hernia although esophagoscopists report that small superficial erosions of the gastric mucous membrane are found fairly frequently in this type of diaphragmatic hernia.[34] The ulcers may or may not perforate. It is obvious that the hernia is more likely to be incarcerated if an ulcer is present than if it is absent. Rude[57] expressed the opinion that the constricting effect of the margins of the diaphragm on the herniated stomach is probably instrumental in the causation and development of the gastric ulcer in the hernia.

VIII. FORAMEN OF MORGAGNI HERNIA

This type of diaphragmatic hernia, also called "parasternal" or "costosternal hernia," occurs fairly infrequently. The parasternal space, Larrey's space or the foramen of Morgagni is a bilateral, retrosternal, muscle-free triangle which is covered by peritoneum below and pleura above. Its three borders are anteriorly the sternum, medially the sternal portion of the diaphragm and laterally the costal portion of the diaphragm. These hernias may be either bilateral or unilateral. Both types have been described.[44] These hernias have a sac. In bilateral hernias there may be stomach on one side and colon on the opposite side (Fig. 9).

Harrington[25] stated that this type of hernia is the least common type of hernia that he has operated on. He also suggested that this type of hernia is essentially congenital in origin although it may not be present at birth. It develops later in life owing to the effect of markedly increased intra-abdominal pressure on a developmental defect in the diaphragm.

The roentgenologic findings are those of the appearance of abnormal shadows near the midline in the bases of the roentgenograms of the thorax (Fig. 10). Shadows in the cardiophrenic angles which do not appear to be completely outlined within the thorax must be differentiated from costo-

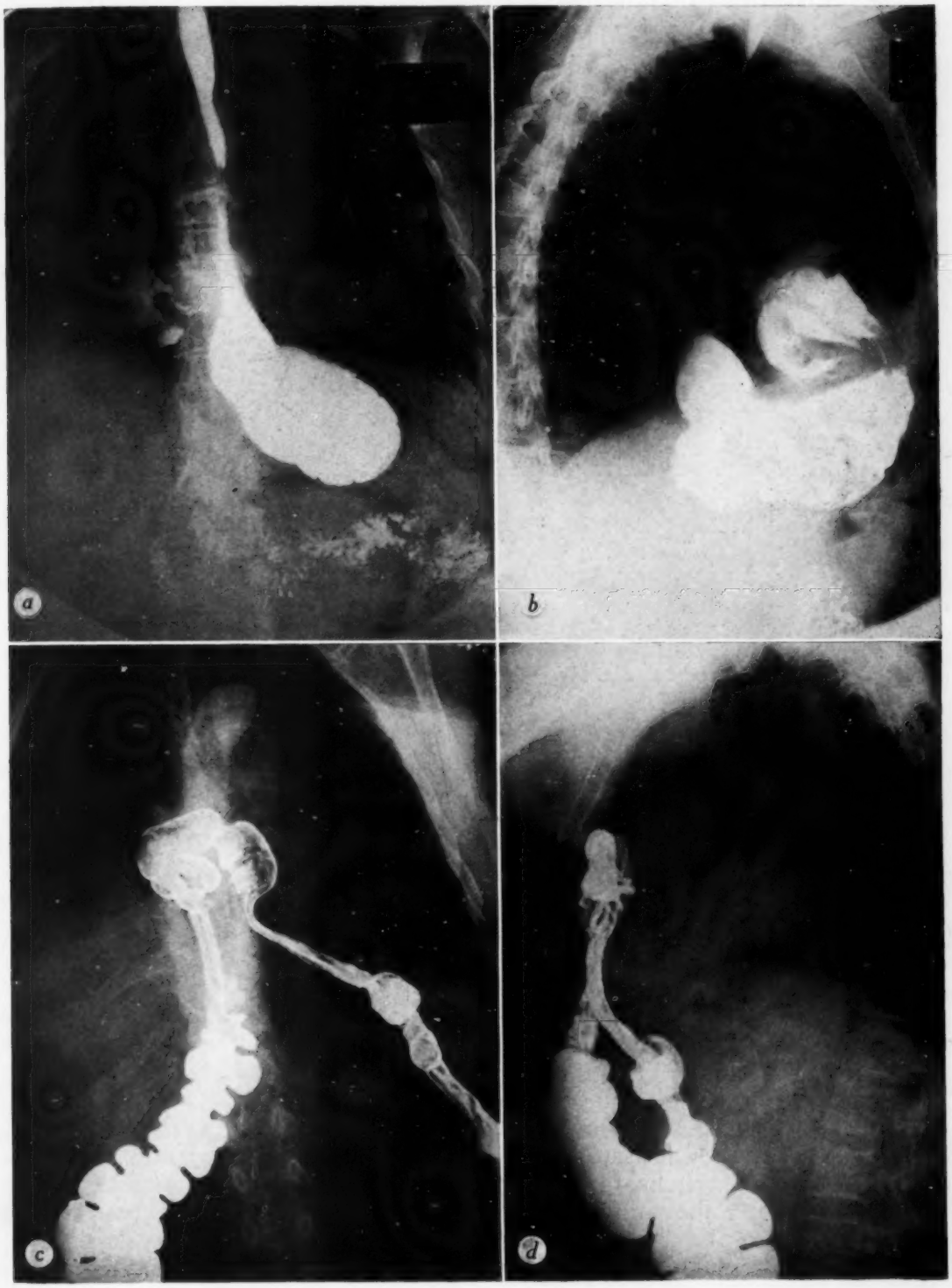

Fig. 9. Bilateral foramen of Morgagni hernias in the case of a fifty-four year old woman. *a.* Pyloric end of the stomach in the right-sided hernia. There is also a small esophageal hiatal hernia. *b.* Lateral view; the pyloric end of the stomach herniating through the right foramen of Morgagni and a small esophageal hiatal hernia. *c.* Colon in a left-sided foramen of Morgagni hernia. *d.* Lateral view; herniation of the colon through the left foramen of Morgagni.

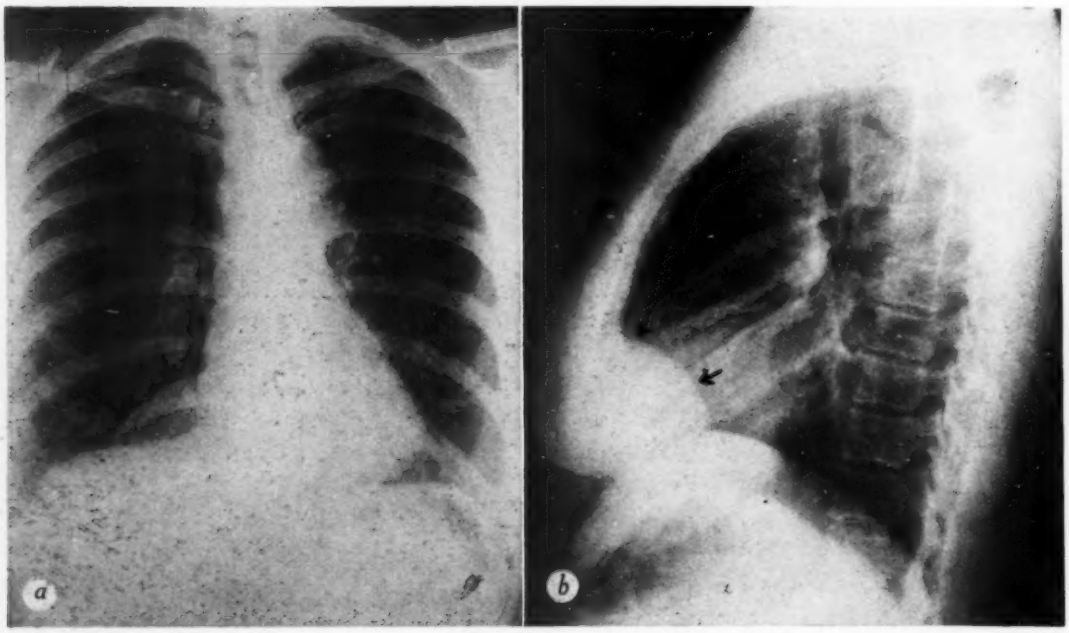

FIG. 10. Foramen of Morgagni hernia in the case of a fifty-one year old woman. *a*. The roentgenogram of the thorax reveals a triangular shadow in the cardiophrenic angle on the right side. The patient had never had any symptoms referable to this lesion; at operation she was found to have a foramen of Morgagni hernia containing omentum. *b*. Lateral view of the thorax. Note the well-circumscribed anterior mass which is not entirely outlined within the thorax.

sternal hernia. A lateral roentgenogram is especially useful in this type of hernia. If the mass is anterior and in close conjunction with the diaphragm, further information may be obtained by the roentgenoscopic examination of the alimentary tract. More frequently this type of hernia contains colon. Occasionally when this type of diaphragmatic hernia contains omentum only, it may simulate closely a pulmonary tumor and it may be impossible to distinguish roentgenologically between tumor and hernia.

The lateral roentgenogram of the thorax may reveal that the contents of the hernia contain fluid and gas which is strong suggestive evidence of the presence of this type of hernia. Frequently the outlines of the colon with its haustral markings may be seen in the anteroposterior roentgenograms of the thorax. This type of diaphragmatic hernia may simulate many types of lesions. It is frequently associated with changes in the lung. Colmers[12] reported a case of right-sided parasternal hernia with acquired total atelectasis of the middle lobe of the right lung. The hernia may simulate fluid in the pleural space, pleural thickening, tumor, atelectasis and many other lesions and it must be considered in the differential diagnosis of most of the lesions occurring in the bases of the lungs. Fortunately the parasternal type of hernia is rare. If there is sufficient reason to suspect the lesion, examination of the intestinal tract with opaque mediums will usually be of help in arriving at a diagnosis.

IX. PLEUROPERITONEAL HERNIA

This type of diaphragmatic hernia, also called hernia through the foramen of Bochdalek, is a hernia through the posterior segment of the diaphragm. Developmentally this is a weak spot and a point of fusion in the membranous diaphragm. In the early embryologic development of the diaphragm the pleuroperitoneal canals are located in this region. These provide a communicating

canal between the peritoneal and pleural cavities. Normally these canals close by ingrowth from their walls to form the pleuroperitoneal membrane. If the pleuroperitoneal canals should remain open, then the increased intra-abdominal pressure would force viscera into the thoracic cage and a so-called false hernia would occur. However, if the pleuroperitoneal canals close and a hernia occurs in this region then the sac would be made up of layers of pleura and peritoneum and a true hernia would result. This weak spot in the diaphragm persists as the muscular elements invade the diaphragm because it then becomes the junction for two separate muscular elements.

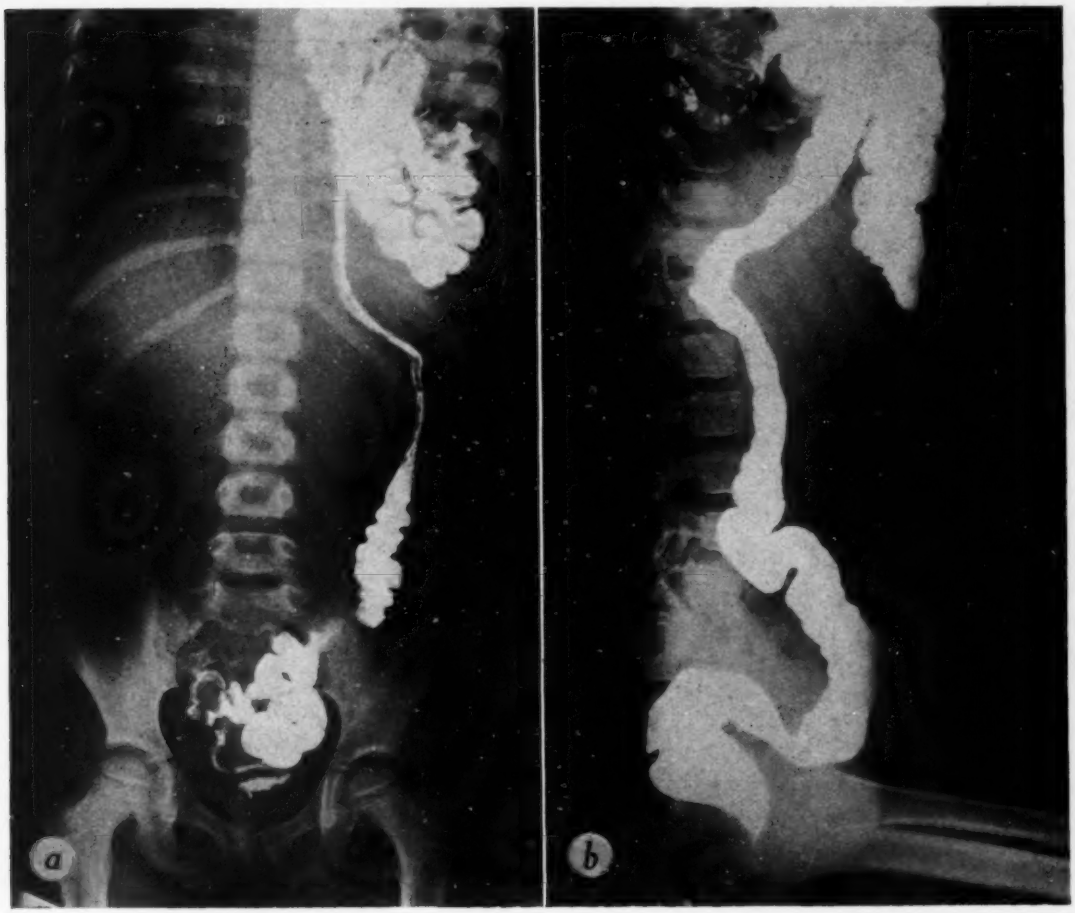

Fig. 11. Pleuroperitoneal hernia in the case of a one year old girl. *a*. Segment of colon above the left diaphragm. At operation the colon and small bowel were found to be herniated through a fairly small opening at the pleuroperitoneal hiatus. *b*. Lateral view of the thorax. Note the numerous loops of small intestine.

These hernias are present at birth. Harrington[24] has stated that many infants suffering from this condition die in the first few days of life because of respiratory and cardiac embarrassment before treatment can be instituted. Carter[26] in discussing an article by Harrington stated that 75 per cent of infants who have congenital hernia through the diaphragm die before the end of the first month of life. A further number of the remaining 25 per cent die early in childhood. The importance of early diagnosis cannot be overemphasized. Respiratory or cardiac embarrassment in newborn infants is usually sufficient indication for roentgenographic examination of the thorax and the possibility of congenital diaphrag-

matic hernia must always be kept in mind by the roentgenologist.

Several cases have been described in which the patient was an adult. Commonly these patients complain of epigastric pain which may be associated with gastrointestinal upsets or constipation. The contents of this type of hernia most frequently encountered are colon, small bowel and sometimes spleen and stomach. Pleuroperitoneal hernias may occur on either the right or the left side.

Roentgenograms of the thorax are important in diagnosis. These hernias are located posteriorly. Shadows in which the continuity is incomplete above the diaphragm may very possibly be pleuroperitoneal hernias. Frequently a pleuroperitoneal hernia will have the appearance of an abscess or cysts of the lower lobes of the lungs. Bizarre shadows in the roentgenogram located behind the heart must be considered as possible hernias. Sometimes the haustral markings of the colon or small bowel may be visible in the roentgenogram of the thorax.

Roentgenoscopic examination of the stomach, small bowel and colon should be done in suspected cases, to attempt to determine the contents of the hernia and its type and location (Figs. 11 and 12). Diaphragmatic motion may be affected on the side of the hernia and the diaphragm should be carefully examined by means of roentgenoscopy in order to aid in both diagnosis and differentiation.

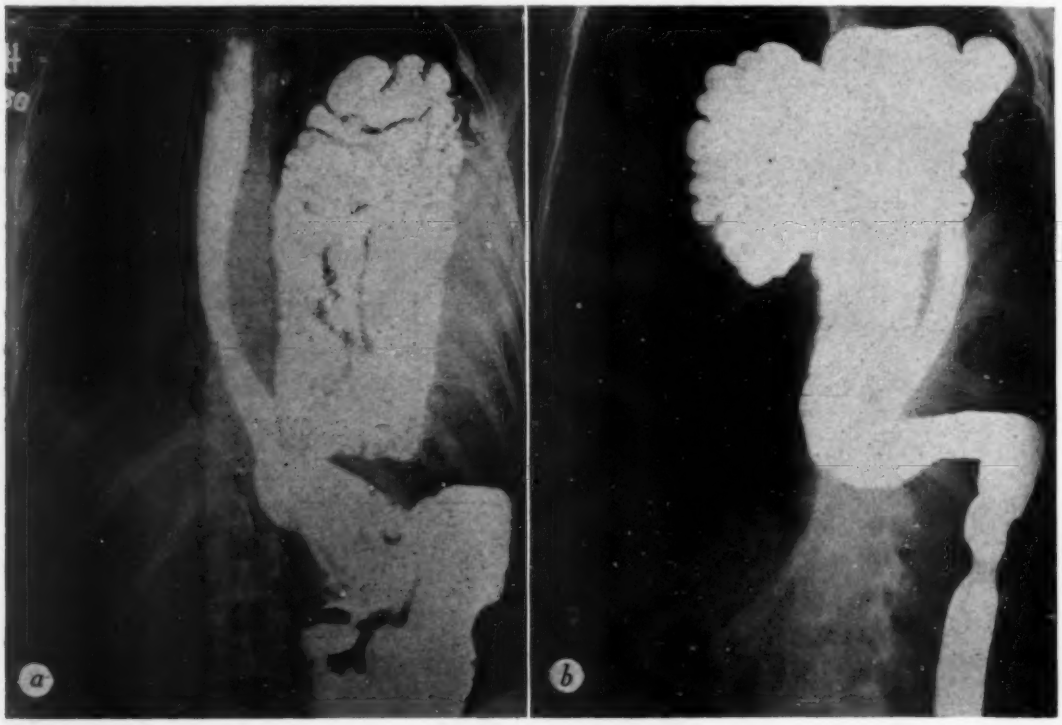

FIG. 12. Pleuroperitoneal hernia in the case of a twenty-nine year old woman. *a*. Large amount of small bowel above the diaphragm. At operation it was found that the pleuroperitoneal membrane had completely failed to develop with a resultant defect in the posterior segment of the diaphragm. The stomach is in normal position below the diaphragm. *b*. Oblique view; transverse colon, ascending colon and numerous loops of small intestine above the left diaphragm.

X. CONGENITAL DEFECTS IN THE DIAPHRAGM

This group of hernias includes all congenital hernias which are not included under the esophageal hiatal group, the foramen of Bochdalek and the foramen of

Morgagni hernias (Fig. 13). Failure of development with defect in the diaphragm has been reported in nearly every segment of the diaphragm. Congenital defects, however, seem to be more prevalent on the left side than on the right.[49]

genologic examination of the thorax. Abnormal shadows, especially in the left region of the diaphragm, must be thoroughly investigated before they are dismissed from consideration. Lateral roentgenograms of the thorax may be useful here

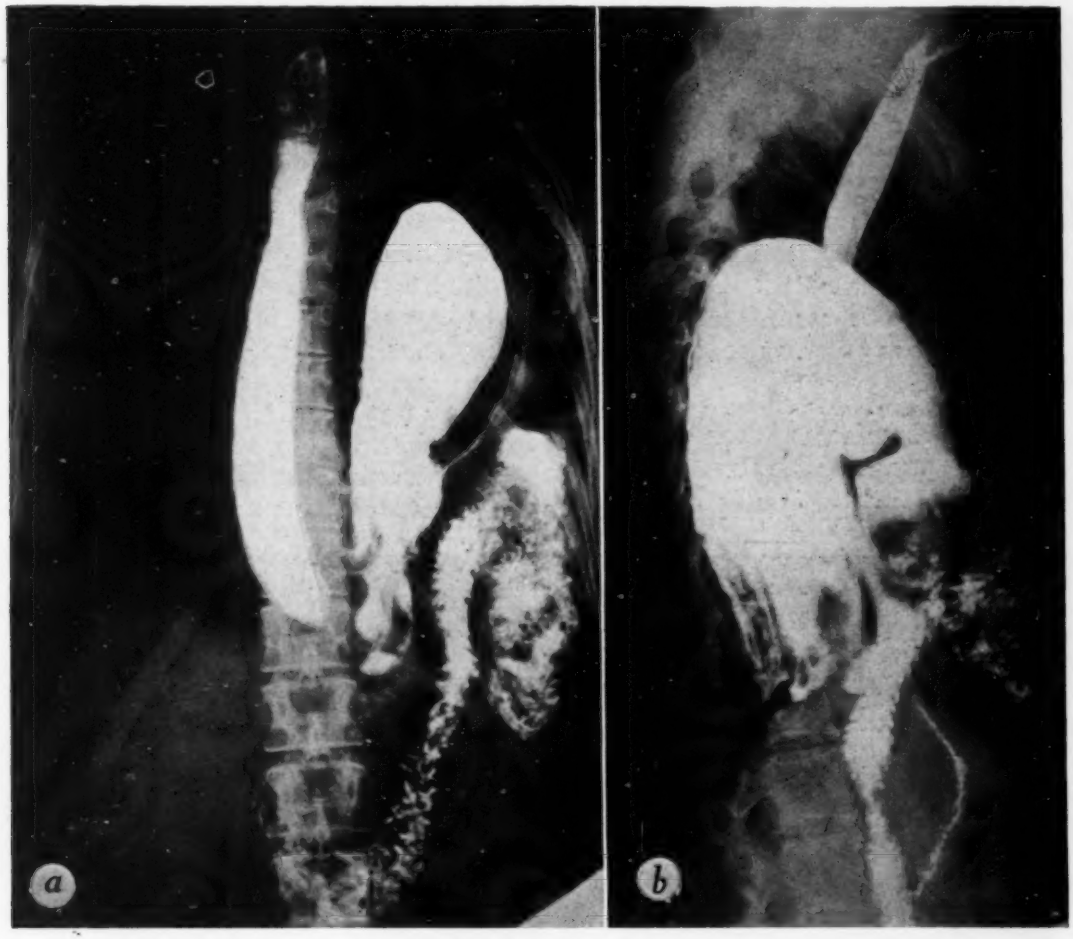

Fig. 13. *a*. Stomach and a portion of small bowel of a forty-four year old woman who had congenital absence of the posterior half of the diaphragm on the left. The hernia contained stomach, colon and small bowel. *b*. Lateral view of the stomach.

In many of these cases the patients are newborn infants with developmental defects in the diaphragm. Rawes,[51] Swope,[61] Kerr and Steinberg,[39] Bradley, Zulich and McKee,[8] and Keith[38] have reported cases in which congenital defects in the diaphragm were present in infants and children.

The roentgenologist again must be on the alert for these lesions in the routine roentgenologic examination of the thorax. Abnormal shadows, especially in the left region of the diaphragm, must be thoroughly investigated before they are dismissed from consideration. Lateral roentgenograms of the thorax may be useful here again. The observation of any suspicious shadow in the diaphragmatic region should indicate further examination by means of opaque mediums and roentgenoscopy to differentiate the nature of the lesion. These hernias may contain stomach, colon, small bowel and spleen and adequate roentgenoscopic investigation of these involved viscera must be carried out.

In newborn infants it is especially im-

portant to consider the possibility of diaphragmatic hernia. A routine roentgenogram of the thorax might lead to a diagnosis which would save the infant's life by presenting evidence of hernia which would warrant further investigation by means of opaque mediums which could prove the diagnosis. This is an especially difficult group of patients to handle. However, the frequency with which roentgenograms of the thorax are obtained in infants who have cardiac or respiratory embarrassment is increasing and it is very probable that the diagnosis can be made much more often. Carter and Harrington in discussing an article by Harrington[29] have pointed out that too many of these infants die without benefit of treatment that could save their lives.

XI. CONGENITAL ABSENCE OF THE HEMIDIAPHRAGM

Congenital absence of the left half of the diaphragm was described by Harris and Clayton-Greene[28] in 1912. In their case the patient was a woman thirty-one years old. A diagnosis of diaphragmatic hernia was made by means of opaque bismuth mediums and roentgenoscopic examinations. The patient was operated on and found to have congenital absence of the left hemidiaphragm. This illustrates why it is important that congenital absence of the diaphragm be considered in the diagnosis of diaphragmatic hernia. Jenkinson[36] has also emphasized this point in an article on this subject. LeWald[41] stated that there are probably a considerable number of cases of complete absence of the left half of the diaphragm which have been recorded as diaphragmatic hernia.

In many of the cases of congenital absence of the hemidiaphragm the patients die in infancy but a number of these patients live to adult life. Jenkinson[36] in 1931 reported that there were 14 cases in the

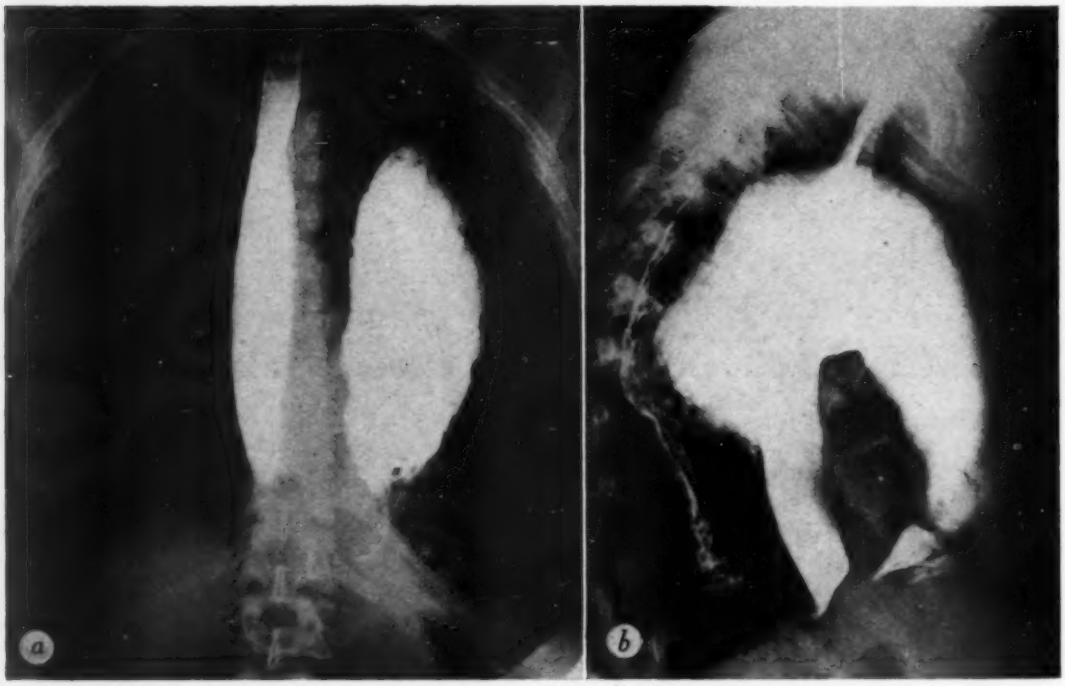

FIG. 14. Posttraumatic diaphragmatic hernia in the case of a thirty-four year old man. *a*. Stomach and colon in left side of the thorax. Three years before admission the patient had been in an automobile accident, in which he was doubled up under a car. At operation the diaphragm was found to be torn from one-half of the thoracic wall posteriorly, and stomach, colon, spleen, small bowel and left kidney were found within the left side of the thorax. *b*. Lateral view to show the stomach.

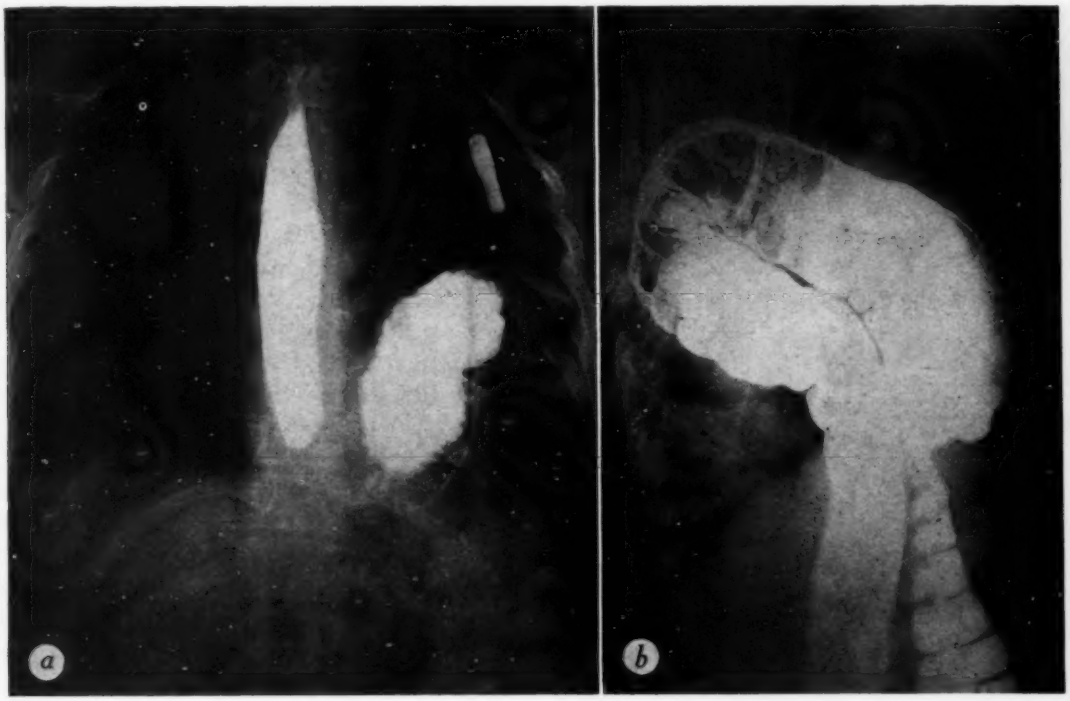

Fig. 15. Posttraumatic diaphragmatic hernia in the case of a twenty-five year old man. *a*. Stomach and colon above the left side of the diaphragm. At operation patient was found to have stomach, transverse colon, omentum, spleen and left lobe of liver in the left side of the thorax. A large laceration of the left side of the diaphragm which was located at the junction of the posterior and middle thirds and which involved two-thirds of the diaphragm was found. One year before admission the patient had received a crushing injury to the thorax in an automobile accident. *b*. Lateral view of the thorax; colon above the diaphragm.

literature in which patients had lived to adult age.

The appearance of the roentgenogram of the thorax may closely simulate that of eventration. Lateral roentgenograms of the thorax may be of some value in determining the location of the diaphragm but it is often extremely difficult to be sure of its location. If it is very thin or very high it can still be readily distinguished in cases of eventration. A lateral view of the thorax to include the diaphragm which shows only one leaf of the diaphragm with no evidence of eventration should suggest congenital absence of the diaphragm or diaphragmatic hernia. Complete absence of the diaphragm will permit bowel and viscera to be present in the thoracic cavity. It is also necessary to differentiate complete absence of the diaphragm from diaphragmatic hernia. In uncomplicated cases this would not be difficult. However, if the hernia has been present for some time and if it is relatively fixed in position with a large amount of bowel in the thorax obscuring the diaphragmatic structure, it may be extremely difficult to differentiate these two conditions accurately.

Roentgenoscopic examination of the diaphragm is extremely important since shadows which simulate the appearance of the diaphragm in cases of congenital absence may be determined by careful roentgenoscopic examination. Jenkinson[36] has stated that occasionally the stomach may simulate the diaphragm but that roentgenoscopic examination of its movements will serve to differentiate it from the diaphragm.

Fortunately, congenital absence of the diaphragm is extremely rare It should, however, be ruled out in cases of large diaphragmatic hernia since there is no method

FIG. 16. Inflammatory necrosis of the diaphragm with diaphragmatic hernia in the case of a fifteen year old girl who had a ruptured appendix with generalized peritonitis followed by empyema. Roentgenograms of the stomach show stomach and colon above the diaphragm. At operation inflammatory necrosis of the diaphragm was noted with three large openings in the diaphragm which measured from 4 to 9 cm. in diameter, and through which the abdominal viscera had herniated.

by which the surgeon can repair congenital absence of the diaphragm.

XII. POSTTRAUMATIC HERNIA

Posttraumatic diaphragmatic hernias may be divided into two groups. The first of these is the traumatic type following wounding by knife or gunshot, a crushing injury or a violent forward flexion of the body. Wounds and injuries due to automobile accidents may replace gunshot and knife wounds as a prime source of traumatic diaphragmatic hernia (Fig. 14). Harrington[26] has stated that the posttraumatic type of hernia may be due either to direct or to indirect injury to the diaphragm. In cases of indirect injury the hernia may occur at any point, including the points of embryologic fusion, but the most common sites are the dome and the posterior half of the left hemidiaphragm. Among the types of indirect injury is the violent forward flexion of the body which acts like crushing a rubber balloon in the fist (Fig. 15). The second type of posttraumatic hernia is the erosion which may develop in the diaphragm following inflammatory necrosis of a segment of the diaphragm (Fig. 16). This may occur in conjunction with subdiaphragmatic abscesses following a surgical procedure within the abdominal cavity.

Traumatic hernias of the diaphragm may occur anywhere in the diaphragm. In the direct type the point of injury determines the location of the hernia. Symptoms usually develop very soon after the injury and the onset of symptoms is almost always directly related to the injury although this may not be always true. In the injury all three layers of the diaphragm are involved. When the viscera protrude through this opening there is no hernial sac, unless there is indirect injury.

The roentgenograms of the thorax should be the starting point in investigation of this type of hernia. We wish to emphasize the importance of the routine roentgenographic examination of the thorax. Any suspicious shadow within the bases of the pleural cavity must be examined with the possibility of diaphragmatic hernia in mind. The clinician can be of great help also if there is obtained a history of injury with subsequent development of symptoms. The lateral view of the thorax may serve to clarify the suspicion or it may not. In any event the definitive diagnosis depends on the examination of the alimentary canal by the use of opaque mediums. Sometimes if the contents of the hernia consist of solid viscera or omentum the diagnosis may be very difficult to obtain. Roentgenoscopy may be of some value, however, and a close and

careful examination of both sides of the diaphragm may lead the examiner to strong suggestive evidence of the diagnosis.

If posttraumatic diaphragmatic hernia is suspected, examination of the stomach, small bowel and colon should be carried out in addition to stereoscopic and lateral views of the thorax.

XIII. EVENTRATION

Eventration of the diaphragn is important because of the necessity of differentiating this condition from diaphragmatic hernia. It is unfortunate that the term "eventration" has been applied to this condition, since it is a misnomer. As Giffin[21] has pointed out, it is not a good term. Surgically it means that a large portion of the abdominal viscera is outside the peritoneal cavity. Obviously this does not occur in eventration. Bayne-Jones[4] has stated that among diaphragmatic lesions, none has had more names attached to it than eventration. If a term which was more accurate could be universally adopted it would simplify matters but since the term "eventration" has been used to describe this condition for many years, it would probably be easier to attempt to establish a definition of eventration which would describe the condition to which common usage has applied the term.

Various definitions have been suggested. One definition suggested is "a thinning out and fatty degeneration of the muscular fibers of the diaphragm and bulging upward of the same to the level of the second or third rib." Sailer and Rhein[59] proposed that eventration be defined as "an abnormally high position of the diaphragm with dislocation upward of the abdominal viscera, especially stomach with hypoplasia of the left lung and dislocation of the heart to the right." In any definition there are two necessary factors: (1) that the hemidiaphragm be elevated to an abnormally high position and (2) that the hemidiaphragm be markedly thinned out.

These two things being present, one could define eventration as a markedly thinned out and highly elevated diaphragm.

The causation of eventration has not been adequately explained. Several hypotheses have been advanced, none of which have gained wide acceptance and none of which seem to explain satisfactorily why eventration occurs.

The pathologic anatomy of eventration has been studied a number of times. The diaphragm on the affected side is described as a thin membrane covered above by pleura and below by peritoneum. Between these membranes, which are normal in appearance, is a thin sheet of fibrous tissue. Within the layer of fibrous tissue a few occasional strands of muscle may be seen. In some cases the muscle strands were found to be replaced by fat cells. There was sometimes a fringe of normal muscle around the costal attachments of the diaphragm, which disappeared as the dome was reached. Examination of the phrenic nerves revealed that they were slightly smaller on the affected side than on the opposite side but apparently normal in every other respect. Necropsy has shown that while the diaphragm may be markedly elevated the lung is not compressed. This is a strong argument in favor of a congenital defect in development of the lung on the affected side or a congenital defect in development of the diaphragm.

The diagnosis of eventration is not an easy one to make. Frequently the diagnosis is presumed when the examiner has satisfied himself that there is no diaphragmatic hernia present. The classic description of eventration is of a markedly elevated diaphragm on the affected side with a high arched smooth contour. The diaphragm may be very highly placed or it may not be. Varying degrees of elevation from the ninth rib in the posterior axillary line to the fifth rib in the posterior axillary line were seen in our series of cases of eventration. The thinning of the dome of the diaphragm with the resultant high arch is characteristic of eventration but the degree of arching is variable and since there is considerable

variation of the shape of the diaphragm in human beings, the high arching curve of the diaphragm is not always seen in cases of eventration. Because of individual variation and because of possible inflammatory reaction as well as a variable amount of muscle function in the small fringe of muscle still remaining in the diaphragm, the contour of the diaphragm in cases of eventration is not always smooth and regular. It may at times be quite irregular.

The motion of the diaphragm in cases of eventration may be one of three types: (1) it may be normal but considerably decreased; (2) it may be paradoxical; (3) there may be no motion at all. If there is any function in the fringe of muscle fibers remaining in the diaphragm a small amount of normal motion may be produced. If there is no function remaining and the diaphragm is free, paradoxical motion will result. If there are adhesions causing fixation of the diaphragm, then it will be immobile.

There is no specific age group. In fact if one accepts the hypothesis that eventration is probably a congenital lesion, then it may be encounterd at any time during life. In most of our cases the age of the patients ranged between forty and sixty years.

Apparently eventration is more frequent among men than among women, in a ratio of about 3:1 (27 per cent in women, 73 per cent in men). This is in agreement with other presentations on the subject.[35]

Eventration is associated with some displacement of the cardiac shadow to the right. This varies in degree but is present in more than 50 per cent of the cases of eventration. We did not find any eventration associated with dexiocardia in our series of cases.

We reviewed 40 cases in which the roentgenographic diagnosis of eventration had been made or suspected. Of these 40 cases we felt that 26 were examples of eventration. There is no specific roentgenographic or roentgenoscopic criterion for the diagnosis of eventration nor does it appear that there ever will be. The diagnosis is not always entirely satisfactory. Analysis of the history and careful examination, both roentgenoscopic and roentgenologic, should give enough evidence to reach somewhere near the truth.

However, more important than the diagnosis of eventration, which may be of academic interest only, is the differentiation between diaphragmatic hernia and eventration. This differentiation is extremely important and usually quite difficult. Many suggestions have been made for the differentiation of eventration from diaphragmatic hernia. Their very multiplicity should suggest that there is no definite specific method by which it is possible to make this differentiation. However, if all of these methods be employed it is reasonable to expect that a positive diagnosis may be aided by one or more of these suggestions. Their limitations should be borne in mind, and it would be unwise to depend entirely on a single method of differentiation.

As was stated before, in the roentgenoscopic examination of patients who have eventration the diaphragm may be immobile, may demonstrate paradoxical motion or may appear to move normally. Various authors have suggested the use of these facts as an aid in differentiation of this condition from diaphragmatic hernia. Unfortunately all three states of the diaphragm may be found in cases of diaphragmatic hernia as well. Thus the motion or lack of motion fails to help. Theoretically, if there were no adhesions, the diaphragm on the affected side in cases of eventration should show some paradoxical movement and a much greater excursion than the normal side. Except in those cases with a small fringe of muscle present it cannot contract since there is no muscle to produce movement and if there is mucular movement, then we are not dealing with true eventration. If there were nothing to complicate the situation such as adhesions and fixation of the diaphragm, then the diaphragm in cases of eventration should show paradoxical movement with considerable excursion, while the diaphragm in cases of hernia moves normally except for a slight paradoxical movement at the

beginning of respiration because it is weakened by the hernia.

The location of pulmonary markings has been suggested also. Obviously, there are no pulmonary markings below the diaphragm in cases of eventration. It is theoretically possible to find them in the region occupied by a hernia.

Another procedure is that suggested by Carman and Fineman.[10] When eventration or diaphragmatic hernia is suspected barium in water is given the patient. The course of the ingested mixture is observed under the roentgenoscope. In cases of diaphragmatic hernia the fluid will assume a higher level than the cardiac orifice of the stomach while in cases of eventration it never goes above the cardiac orifice.

Overholt[48] has listed various tests used in differentiation. Among these is a physical sign involving the movements of the costal margins. Normally the outward excursions of the costal margins are limited by the pull of the diaphragm. In cases of eventration this effect is decreased or absent and a more noticeable excursion is allowed on the involved side than on the opposite side. This would be of value in cases of small diaphragmatic hernia and when used in conjunction with other confirmatory evidence. However, it cannot be definite because with a large hernia or defect in the diaphragm it is no longer reliable.

Sante[60] has suggested the use of pneumoperitoneum as an aid in the differential diagnosis of these two conditions. If air is injected into the peritoneal cavity and the patient is placed in the upright position, the air will collect under the diaphragm in cases of eventration whereas if there is a defect in the diaphragm the air will be found in the thoracic cavity. This would also give some indication of whether the apparent hernia is a true hernia or not. If the air is enclosed in a sac in the thorax then one is dealing with a true hernia. If not, it is not a true hernia and these facts are of definite interest to the surgeon. Walton[63] has also suggested the use of pneumoperitoneum as a differential diagnostic aid. This test is a good one if one can get positive results for hernia. It can be conclusive only if air passes above the diaphragm because, as Reich[52] has suggested, when there are adhesions between the herniated viscera and the diaphragm no definite conclusions can be drawn. Faulkner[18] has suggested another variation of this same idea: the use of pneumothorax as a help in differential diagnosis. If a hernia is present air will pass into the abdominal cavity. Again the same usefulness and the same limitations apply.

Measurement of intragastric pressure has been used by some investigators.[32] The rationale of this method is based on the difference in pressure which obtains in the peritoneal and pleural cavities on respiration and the movement of the diaphragm. If the stomach is in the abdomen the intragastric pressure will rise when the diaphragm descends and fall when the diaphragm ascends. If any part of the stomach is in the thorax the pressure will fall when the diaphragm descends and rise when it ascends. The obvious limitations and the cumbersome apparatus necessary have made this method of little value in differential diagnosis.

Overholt[48] presented a case in which all of these various means of differentiation were tried and no definite conclusions could be reached. Finally the phrenic nerve on the affected side was stimulated by a faradic current. In a case of eventration one would not expect any response, since there is no muscular element to contract unless a small fringe of muscle is present. In a case of diaphragmatic hernia there should be a definite response. In Overholt's case the diaphragm reacted violently. Reich,[52] however, stated that irritation of the phrenic nerve is of no aid in distinguishing between hernia and eventration.

Laparotomy has been done as a means of deciding definitely with what type of lesion one is dealing.

XIV. SUMMARY

Diaphragmatic hernia is not an uncommon condition. Examination for diaphragmatic hernia should be a part of every

gastrointestinal examination. It should be considered in the differential diagnosis of lesions near the diaphragm in the roentgenogram of the thorax. The chief obstacle to the diagnosis of diaphragmatic hernia is the neglect to look for it. The responsibility for diagnosis lies with the reontgenologist and his efforts should be commensurate with his responsibility.

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MYELOGRAPHIC DEMONSTRATION OF AVULSING INJURY OF THE BRACHIAL PLEXUS*

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THE diagnosis of avulsion of the nerve roots of the brachial plexus, or tear of the roots within the intervertebral foramina, from traction injuries about the neck and shoulder usually presents no difficulty. Such a diagnosis is made in upper brachial plexus injuries on the basis of segmental motor and sensory deficit of the fifth, sixth and sometimes the seventh cervical spinal nerves, including paralysis of the serratus magnus, levator scapulae, and the rhomboids, indicating that the lesion in the nerve roots is medial to the emergence of the nerve supply (long thoracic and dorsal scapular nerves) of these muscles. In lower brachial plexus injuries the diagnosis is made on the basis of segmental sensory and motor deficit of the eighth cervical, first thoracic, and sometimes the seventh cervical spinal nerves, plus a Horner's syndrome. Because such lesions are at present thought to be irreparable and therefore have a poor prognosis, a method of verification of such a diagnosis would be of practical importance.

During the investigation of the cause of pain in the arm and hand of a patient with such a lesion, myelographic evidence was found which seemed to us to confirm the diagnosis of avulsion of the nerve roots. The case is therefore reported in the belief that myelography may be of value in the confirmation of the diagnosis of such lesions.

CASE REPORT

A soldier, aged twenty-six, while overseas fell from a moving truck on July 7, 1945. Immediately upon striking the ground the soldier became unconscious and he was unable to give details as to exactly how he struck the ground or as to which direction his neck and shoulders were rotated by the blow. He regained consciousness shortly after the injury and noted a complete paralysis of the left arm from the shoulder down. He was admitted to an overseas hospital where roentgenograms were taken, showing a simple linear fracture of the right fibula, but no fractures in the left arm, the skull, or the cervical spine. The fractured fibula did not require special treatment, and healed satisfactorily. Within a few days after the injury, he noticed gradual improvement in the paralysis of the arm, but continued to have residual paralysis and anesthesia in the forearm and hand. From the time he regained consciousness, this soldier noticed, in addition to the paralysis, a constant aching pain, "like a tooth-ache," along the forearm and into the hand. It had been constant since the day he was injured and kept him awake at night. He stated that the pain radiated along the ulnar side of the forearm, into the little finger, and over the entire dorsum of the hand. It was not aggravated by coughing, sneezing, straining or lifting. Pressure over the brachial plexus did not increase the pain, nor did compression of the cervical spine. The pain was not aggravated by touching the hand, by excitement, loud noise or sudden jars. He found nothing that relieved the pain. Because of the paralysis and pain he was evacuated to the Zone of the Interior, and was admitted to this General Hospital on September 21, 1945, complaining bitterly of the pain in the arm and hand, which he stated had not improved at all since the injury.

Examination showed a well developed, well nourished white male, whose general physical and neurologic examination was negative except with reference to the head and left arm. There was no sensory deficit except in the left arm, and no weakness except in that arm. There was mild Horner's syndrome on the left, manifested by narrowing of the palpebral fissure and slight, but definite, constriction of the left pupil. Examination of the left arm showed no function in the extensor carpi ulnaris, the extensor digitorum communis, abductor pollicis longus, and the extensor pollicis longus and brevis. Further, there was no function in the entire flexor digitorum sublimis and profundus group, in the

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flexor pollicis longus, and in the flexor carpi ulnaris, and no function in any of the intrinsic muscles of the hand. The pronator teres and the flexor carpi radialis were functioning well; the palmaris longus contracted weakly. The brachioradialis and extensor carpi radialis muscles functioned normally. The biceps brachii was weak, and the triceps brachii was very weak, but functioning. Most of the sternal portion of the pectoralis major muscle was not functioning. The latissimus dorsi, rhomboids and levator scapulae, the serratus magnus, and the deltoid were all functioning normally. A careful sensory examination showed areas of anesthesia and hypesthesia as indicated in Figure 1. The skin resistance was abnormally high in the areas indicated in Figure 2. This of course signified complete absence of sweating in these areas.

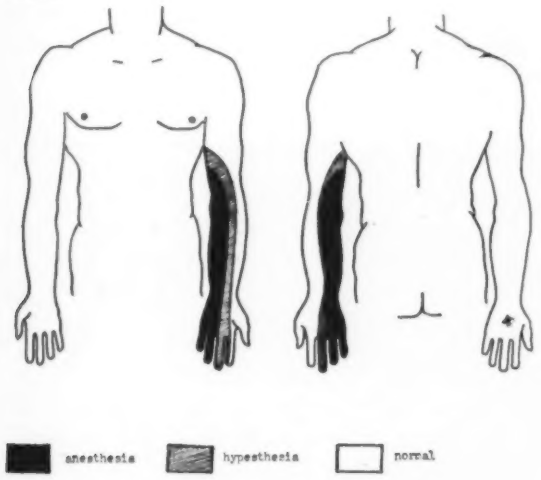

Fig. 1. Sensory examination, showing a sensory deficit in areas supplied by the seventh and eighth cervical and first thoracic nerve roots.

Roentgen examination of the chest, shoulder, and cervical spine failed to reveal any definite abnormalities. Routine laboratory examinations of the blood and urine and the serology were normal.

It was the impression, from the motor and sensory findings, that this man had an avulsion of the seventh and eighth cervical and first thoracic roots of the brachial plexus, and therefore that no neurosurgical procedures to repair the nerves would be of value. The pain presented a difficult diagnostic problem. It was felt that it had none of the stigmata of causalgia, nor did it have any of the features suggesting a herniated nucleus pulposus or scalenus anticus syndrome. There was no cervical rib demonstrated by roentgen examination, and there were no abnormalities noted in the first rib. However, procaine block of the left stellate ganglion was carried out on two occasions with complete relief of pain for fifteen to thirty min-

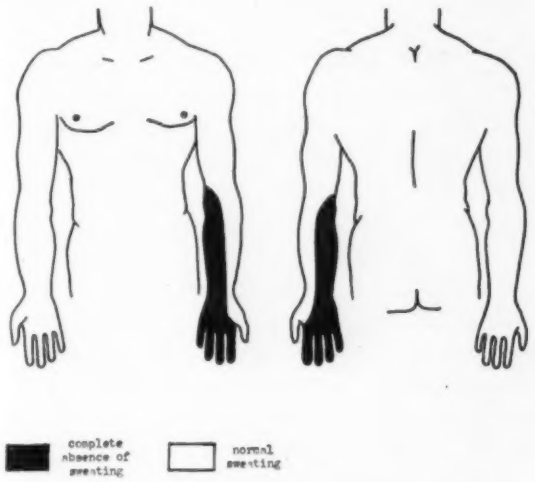

Fig. 2. Dermometer examination, indicating area of de-sweating produced by injury (test done prior to sympathectomy).

utes. Still, it was not felt with any certainty that sympathectomy would offer relief.

A cervical myelogram was made in order to rule out the presence of a herniated nucleus pulposus in the cervical region. This failed to reveal any evidence of a cervical disc. However, it gave a very striking demonstration of what are believed to be traumatic meningoceles at the level of the seventh and eighth cervical and first thoracic nerve roots. The pantopaque appeared to enter the upper dorsal and cervical region normally. However, it was immediately noted that all the nerve sheaths of the left were absent and a linear filling defect was present (Fig. 3). The linear defect measured approximately 3 to 4 mm. in width and extended from the level of the third cervical vertebra down to and including the first dorsal vertebra. The left lateral border of the opaque column was straight and smooth. The cervical pulsations were normal. After several minutes of observation a small drop of the opaque material was seen to detach itself from the main column and migrate laterally into a pouch-like structure in the region of the left intervertebral foramen between the sixth and seventh cervical vertebrae. Immediately thereafter, other drops of the opaque material were detached and also migrated laterally in this region, and in the region

FIG. 3. Cervical myelogram showing opaque column in the cervical region.

of the intervertebral foramina between the seventh cervical and first dorsal, and between the first and second dorsal vertebrae. These also collected in a pouch or diverticulum-like structure. The droplets seemed to be forced laterally by the cervical pulsation. At no time was a connection seen between the lateral collections and the main opaque column. They were always separated by the linear defect. The pouches were completely filled at the end of approximately ten minutes (Fig. 4). The lateral collections in no way resembled lateral extension of the opaque material within a nerve sheath. When the patient was placed in the upright position the main opaque column moved out of the cervical region in a normal manner, but the lateral collections remained (Fig. 5). Films of the cervical region on the following day showed no pantopaque in the cervical region either in the normal subarachnoid space or in the out-pouchings. The right side appeared normal.

Because of the severity of the pain and the relief obtained from procaine block of the stellate ganglion, it was felt that this patient should be offered a dorsal sympathectomy, despite the fact that his pain syndrome was *not* causalgia and despite our lack of assurance that the operation would relieve the pain. Laminectomy was not considered advisable, first, because the lesions in the nerve roots were felt to be irreparable; and, second, because it was not believed that the meningoceles were causing any pressure on the remains of the nerve roots. After explanation of the entire situation to the patient, he chose to have the operation. Therefore, a dorsal sympathectomy (modified Smithwick) was performed. The postoperative course was uneventful except for the presence of a pneumothorax secondary to air having entered the pleural space at surgery. However, the lung reëxpanded satisfactorily and his postoperative condition was good at all times. Six weeks after sympathectomy the patient stated that his pain had not been significantly improved by the

FIG. 4. Cervical myelogram showing lateral collections of pantopaque.

operation. It was not now constant, but occurred on frequent occasions and, when present, was as severe as it was prior to surgery. The cause of his pain is still undetermined. There has been no change in the motor and sensory examination since admission to this hospital six months ago.

COMMENT

The motor and sensory paralyses presented by this patient seem entirely consistent with the diagnosis of avulsion of the seventh and eighth cervical and first thoracic nerve roots of the brachial plexus. A portion of the preganglionic sympathetic fibers to the eye were interrupted by this avulsion, since they emerge at least in part from the spinal cord via the first thoracic nerve root. Since the preganglionic fibers to the arm emerge from the cord through the second thoracic nerve root and those situated more caudally, probably none of these were interrupted in this case. The skin resistance findings in the left arm are probably the result of tearing of the seventh and eighth cervical and first thoracic nerves and the grey rami coming to them from the ganglionated sympathetic chain. This then is a postganglionic interruption.

It must be pointed out that the myelographic findings are probably those of a rupture of the meninges in the region of the seventh and eighth cervical and first thoracic nerve roots, thus allowing the opaque material employed in the myelogram to escape from the subarachnoid space in these areas. The material thus presumably flowed into three spaces, which were occupied by the seventh and eighth cervical and first thoracic nerve roots prior to their avulsion. The term "traumatic meningocele" has been employed here as one of convenience, although of course we have no way of knowing that these out-pouchings are actually lined by the meninges. Although we have not visualized these areas surgically in this patient and thus have not established with certainty this diagnosis, the striking myelographic findings, coupled with the clear neurological findings, make the above interpretation seem very probable.

FIG. 5. Cervical myelogram showing lateral collections remaining after the column of pantopaque had been removed from the cervical region.

The practical importance of the demonstration of such an avulsion is obvious. Without it, one would probably be forced to wait a period of twelve to eighteen months before proceeding with reconstructive surgery of the wrist and hand—for only by waiting would one know with certainty how much return of function might ensue. With this demonstration, however, it seems highly probable that there will be no retrun of function in the paralyzed muscles innervated by the seventh and eighth cervical and first thoracic nerves. Reconstructive surgery will thus be undertaken promptly in order to give the patient, so far as possible, a useful hand.

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PHYSIOLOGICAL STASIS: A CAUSE OF CHOLECYSTOGRAPHIC ERROR*

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SINCE the advent of cholecystography in 1924 the diagnosis of gallbladder disease has become extremely simple and accurate. Yet false cholecystographic findings occasionally lead to unwarranted diagnoses and unnecessary surgery. This paper will discuss an important but frequently neglected cause of cholecystographic error—physiological stasis of the gallbladder.

Non-visualization of a normal gallbladder is probably more frequent than most papers concede. Statistical evaluation based upon operative confirmation may be misleading because factors unconcerned with cholecystography enter into the selection of patients for surgery; most patients with an erroneous roentgen diagnosis of poorly functioning gallbladder will not be suitable for surgical treatment.

These errors should not be dismissed with the statement that diagnosis must depend also on clinical findings; all accept the dictum that cholecystography is not a test for cholecystectomy. The error is equally real whether or not laparotomy is performed, and a grave injustice is done when a patient is placed on an unnecessary medical regimen. The real problem is to eliminate such errors or to recognize situations in which the examination is unreliable.

FIG. 1. Very faint gallbladder shadow eight hours after intravenous administration of sodium tetraiodophenolphthalein. *Case History.* A white male, aged thirty-four, had been acutely ill for several days with severe right upper quadrant pain and vomiting. There was fever and leukocytosis and the attending surgeon's diagnosis was acute cholecystitis. Oral cholecystography revealed no concentration of the dye; re-examination by the intravenous method produced faint gallbladder shadows, definitely not normal. Laparotomy disclosed a grossly normal gallbladder and a perforating gastric ulcer. The greatly decreased gallbladder function demonstrated by intravenous cholecystography can be explained only on the basis of physiological stasis secondary to vomiting and lack of food prior to examination.

BILIARY PHYSIOLOGY

Cholecystography is actually a roentgen demonstration of gallbladder physiology; when pathologic physiology is demonstrated the deduction follows that pathologic anatomy is present.

When bile is excreted by the liver into the hepatic and common duct, sustained contraction of the sphincter of Oddi prevents the bile from passing into the duodenum, but it can pass through the cystic duct into the gallbladder, where fluid is rapidly absorbed and the bile is concentrated. Thus the gallbladder can contain the entire liver output for a twenty-four hour period, at the end of which time it is filled with a thick concentrate of bile salts, pigment, and mucin. Upon proper stimulation the gallbladder is capable of self

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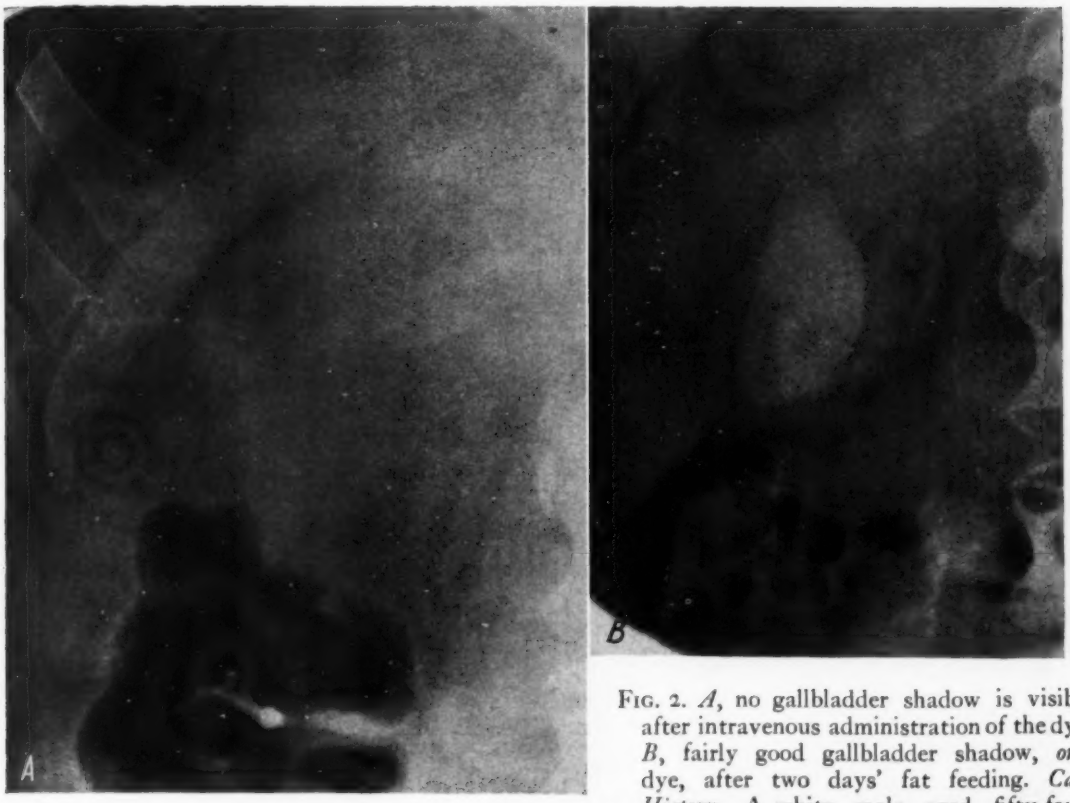

Fig. 2. *A*, no gallbladder shadow is visible after intravenous administration of the dye. *B*, fairly good gallbladder shadow, *oral* dye, after two days' fat feeding. *Case History.* A white male, aged fifty-four, hospitalized because of severe right upper quadrant pain of one day's duration and nausea and vomiting of three days' duration. The patient had complained of right upper quadrant pain and vague gastrointestinal symptoms for one year, and had been on a fat free diet; he had not had previous roentgen examination. At this time the family physician's diagnosis was acute cholecystitis. Cholecystography by both oral and intravenous methods revealed no definite gallbladder shadow, but in view of the above dietary history re-examination after fat feeding was recommended. Two days later *oral* cholecystography revealed a gallbladder of fairly good density. Gastrointestinal study the following day disclosed a duodenal ulcer with evidence of localized perforation, a diagnosis which was later confirmed at laparotomy. The original nonfunction of the gallbladder was probably due to physiological stasis. This contention is supported by the normal response after a short period on fat diet, and at laparotomy a grossly normal gallbladder was found.

evacuation, fat being the only food which will bring about this action.

Certain radiopaque substances are excreted in the bile; roentgen visualization of the gallbladder depends upon subsequent concentration of the dye-laden bile in that organ. Now, if a patient has been limited to a completely fat free diet or has been unable to retain any food, the gallbladder may not have emptied for several days. The bile will be thick and concentrated. When cholecystography is attempted in the presence of such physiological stasis. fresh dye-laden bile is unable to enter the gallbladder; it does not function and it does not visualize, just as though pathologic changes were present. In other cases partial concentration of the dye results in a faint shadow.

MATERIAL

The cases reported were selected from a series of 500 consecutive cholecystograms using priodax, the commercial name for beta-(4-hydroxy-3,5-diiodophenyl)-alpha-phenyl-propionic acid. The first 150 patients in the series included 46 who were also examined by means of intravenous sodium tetraiodophenolphthalein, as a check when the gallbladder was not adequately visualized by the oral method. That series has been previously reported[1]

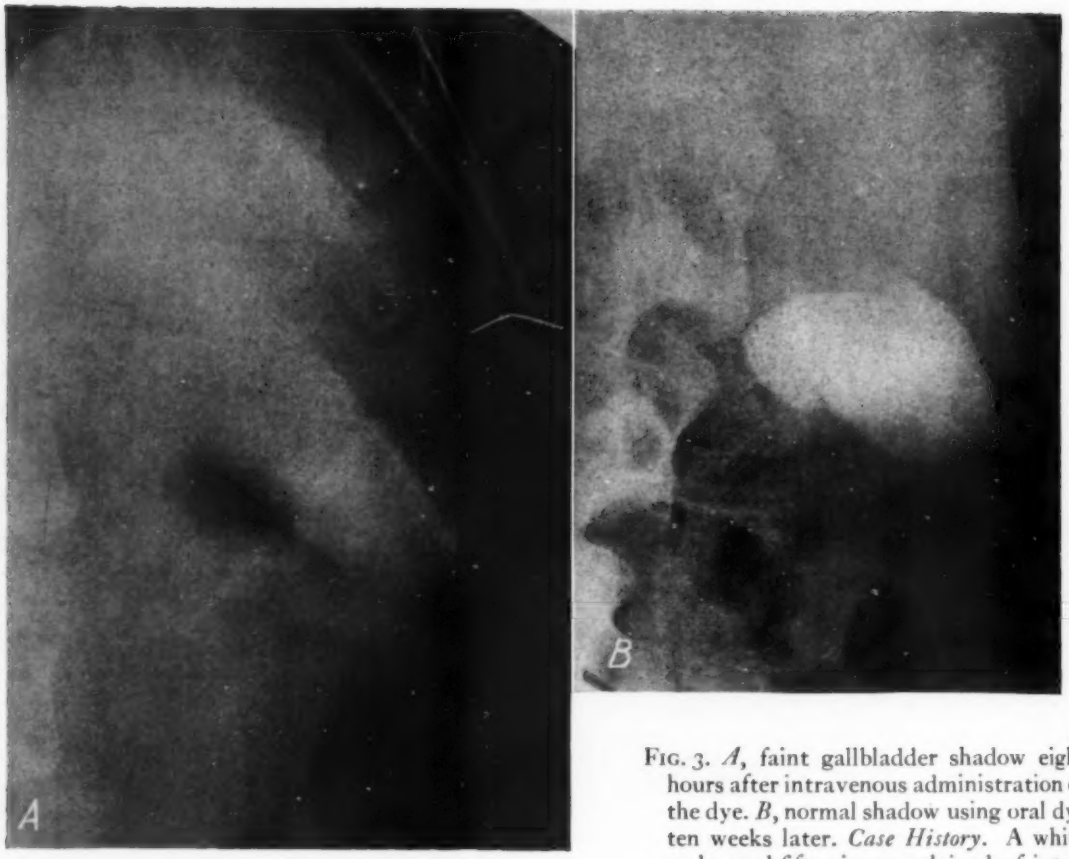

Fig. 3. *A*, faint gallbladder shadow eight hours after intravenous administration of the dye. *B*, normal shadow using oral dye ten weeks later. *Case History.* A white male, aged fifty-six, complained of intermittent epigastric pain and vomiting for four days prior to cholecystography. Examination with priodax disclosed no definite gallbladder shadow, and re-examination by the intravenous method revealed a very faint shadow. It was suggested that the decreased function could be due to physiological stasis rather than gallbladder pathology. Gastrointestinal study with a small quantity of barium revealed pronounced gastric residue which precluded satisfactory examination of the stomach. There was small intestinal distention and hypomotility. Barium enema revealed a sharply localized constriction of the sigmoid colon, not typical of carcinoma. Laparotomy disclosed this was due to adhesions, which were released, and the patient made an uneventful recovery. Re-examination of the gallbladder at a later date revealed normal concentration of the dye. It is probable that the non-function as determined by intravenous cholecystography was due to physiological stasis.

with particular reference to and discussion of discrepancies in the results. It was apparent that discrepancies were due to physiological stasis and that this is a more significant factor in oral than in intravenous cholecystography. However, cases reported here will show that the intravenous method is also subject to this limitation (there is no duplication of cases reported in the two papers).

TECHNIQUE

Meticulous roentgen technique is imperative. Of utmost importance is equipment capable of short exposures, preferably using the rotating anode tube and the fast Potter-Bucky diaphragm.

The evening before examination six 0.5 gm. priodax tablets are swallowed whole during the course of a completely fat free evening meal. The patient may have water until bedtime but is allowed nothing by mouth after midnight. He reports to the roentgen department the next morning and at fifteen hours the first films are exposed. The roentgenologist sees the films, interviews the patient, and outlines subsequent procedures. Cholecystograms in oblique or

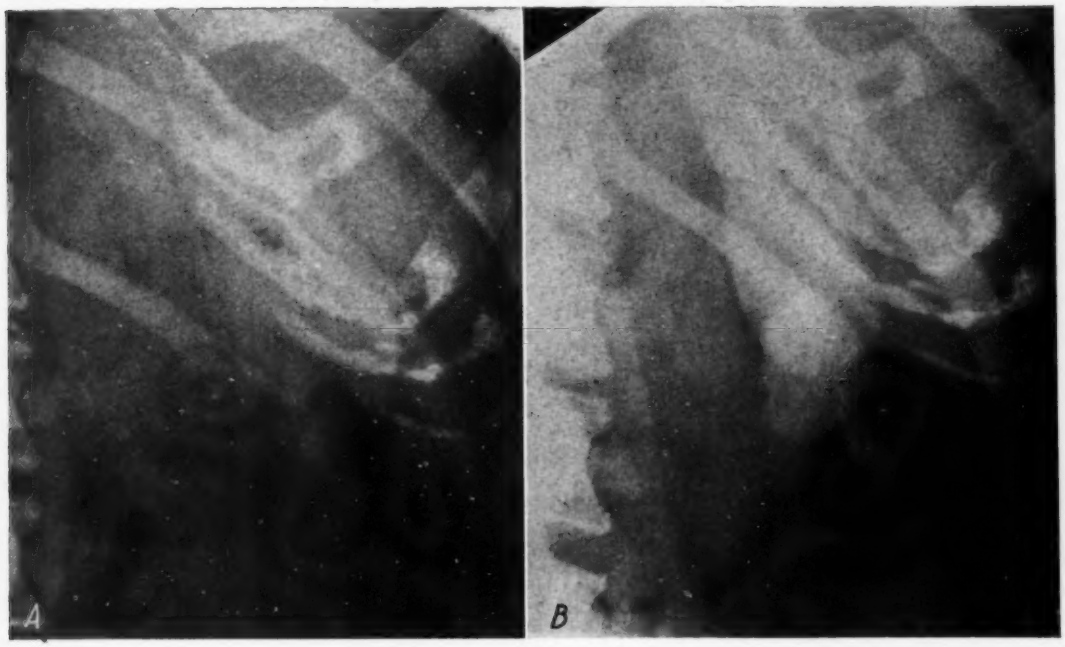

FIG. 4. *A*, oral cholecystogram revealing poor concentration. *B*, normal concentration four days later. *Case History.* This white female, aged forty-one, complained of right upper quadrant pain of five years' duration. She had been on a fat free diet for many months. Oral cholecystography revealed very faint shadows and poor concentration of the dye, and in association with the history this might have been considered adequate evidence of cholecystitis. However, after five days on a high fat diet, re-examination resulted in a gallbladder shadow of normal density.

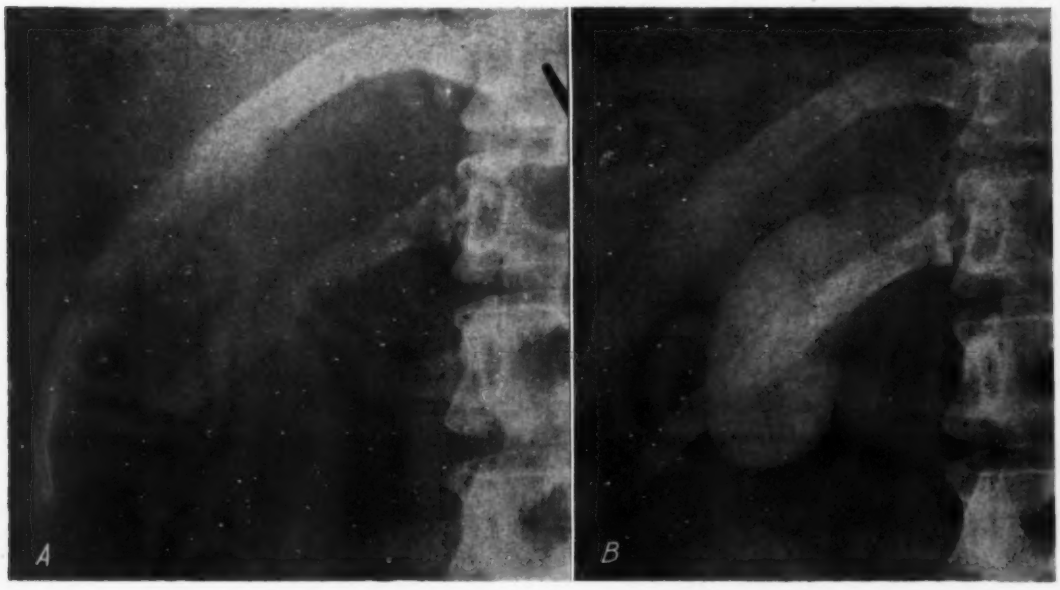

FIG. 5. *A*, priodax cholecystogram showing very faint gallbladder shadow. *B*, satisfactory concentration three weeks later. *Case History.* A white female, aged thirty-nine, complained of upper abdominal pain of several days' duration (not typical of cholecystitis), and nausea and vomiting. The oral dye was retained without vomiting, but the gallbladder shadow was extremely faint. Re-examination after three weeks on a high fat diet resulted in fairly good concentration of the dye.

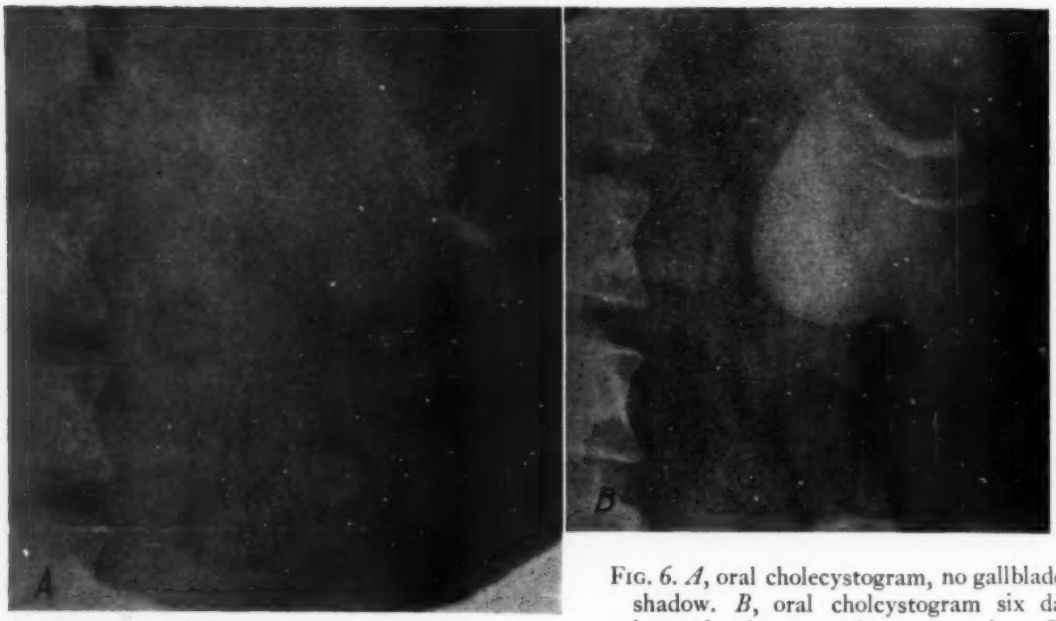

FIG. 6. *A*, oral cholecystogram, no gallbladder shadow. *B*, oral cholcystogram six days later showing normal concentration. *Case History.* A white female, aged forty-eight, was examined with priodax following two weeks of generalized abdominal pain, nausea, and vomiting, during which time she had eaten very little. No definite gallbladder shadow could be demonstrated. After six days on a high fat diet re-examination revealed a normal gallbladder shadow.

erect positions, or with compression, or at a later hour may be requested. Since the patient is fasting, a barium meal study may be started without delay if further gallbladder examination is not necessary.

DISCUSSION

Papers on cholecystography often enumerate certain conditions other than cholecystitis which may cause non-visualization, but rarely is physiological stasis included. Nevertheless this is not a new concept. Curl's[2,3] studies on over 400 normal subjects offer convincing evidence that the diet prior to examination does influence the response to the dye. He concluded that patients on a fat free or low fat diet may have a gallbladder so distended with thick concentrated bile it is unable to admit fresh dye-laden bile, hence will not be visualized on roentgen examination.

Other authors who have given the problem some consideration include Whitaker,[7] who reported finding a normal gallbladder filled with thick concentrated bile after non-visualization by the intravenous method. Robinson[6] recommended the routine administration of a fat meal three hours prior to ingestion of the dye. Jenkinson[5] advocated that all patients with non-visualization be re-examined after a month during which time a diet rich in fats should be given. Feldman[4] suggested a diet consisting of eggs, milk, cream, and other foods should precede the administration of dye, in order to prevent excessive concentration of bile which may result in faint shadows or non-filling.

The case histories in this report offer further evidence that diet prior to cholecystography has a profound influence. It should be noted that in the first 3 cases both oral priodax and intravenous tetraiodophenolphthalein were used, so there should be no question as to absorption of the dye.

Physiological stasis should always be considered when evaluating non-visualization of the gallbladder, and it is of even more importance when the shadows are faint. When there is history of fat free diet or vomiting and limited food intake prior to examination, a faint shadow is of indeterminate significance, and non-visualization must be viewed with suspicion.

Procedures which will eliminate or re-

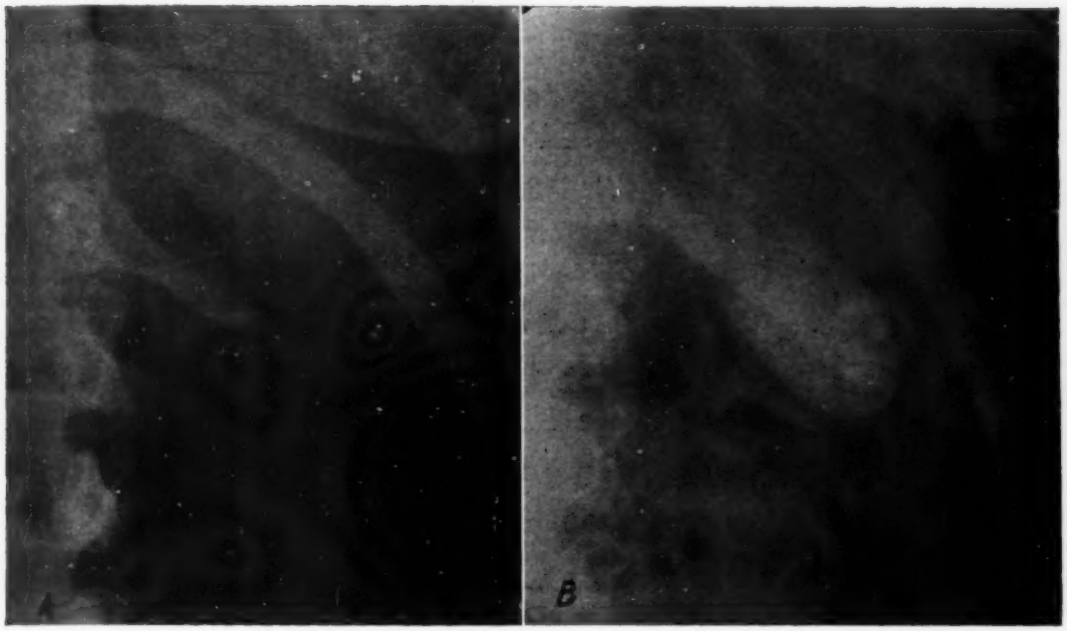

Fig. 7. *A* very faint gallbladder shadow, oral cholecystography. *B*, normal shadow two days later. *Case History*. A white female, aged twenty-nine, complained of attacks of severe abdominal pain of indefinite character. She had been on a fat free diet several days prior to oral cholecystography; the shadows were very faint. After two days on a high fat diet a normal cholecystogram was obtained.

duce these errors are obvious. When possible we insist that the patient have a fatty meal at noon the day before examination; in addition to any food desired, he must take one pat of butter, one soft boiled egg, and one glass of half milk and half cream. It is obvious that the fat meal must be given early enough to complete its action before ingestion of the opaque medium. In questionable cases re-examination after fat feeding will eliminate a significant source of error.

The routine preliminary fat meal was initiated near the middle of this series and has in no way interfered with the examination. On the contrary, there was a sharp decrease in doubtful cases requiring re-examination.

CONCLUSIONS

1. Physiological stasis of the gallbladder may occur when a patient has eaten no fats for a period of twenty-four hours or more. The gallbladder is filled with a thick concentrated bile.

2. Physiological stasis may cause non-visualization of a normal gallbladder because fresh dye-laden bile is unable to enter.

3. A preliminary fat meal will decrease errors due to physiological stasis.

4. Re-examination after fat feeding is a helpful procedure in evaluating the faint gallbladder shadow.

209 Professional Bldg.
Pasadena 1, Calif.

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ROENTGEN APPEARANCE OF DOUBLE GALLBLADDER SIMULATED BY GALLBLADDER WITH CONGENITALLY FOLDED FUNDUS*

CASE REPORT

By RALPH E. ALEXANDER, M.D.
ROCHESTER, NEW YORK

DOUBLE gallbladder is a well recognized but rare congenital anomaly. In spite of its infrequent occurrence, this condition has assumed clinical importance as a result of case reports demonstrating duplication of the gallbladder in which one fundus was diseased while the other gallbladder remained normal both clinically and roentgenologically (Wischnewsky and Braun, quoted by Golob and Kantor[7]). It is, therefore, essential that the true anatomical state be demonstrated by cholecystography prior to operation.

Since the Graham method for visualization of the gallbladder was developed, 9 cases of double gallbladder have been reported as visualized by this method.[2,3,4,5,6,7,8] In some of these cases, the diagnosis was made by roentgenological examination without anatomical confirmation. A case has recently been encountered in which the roentgenograms fulfilled many of the roentgenologic criteria for double gallbladder (Fig. 1). However, further study, including lateral roentgenograms of the gallbladder area, definitely indicates that the anomaly in this case belongs to the category of "folded fundus" and not to that of a double gallbladder. As may be seen in Figure 2, the lateral roentgenogram shows a fundus folded upon itself, dividing the gallbladder into two major components, each of which was sufficiently well marked to produce its own independent shadow and thereby simulate a double gallbladder on the posteroanterior roentgenograms. This type of gallbladder clearly falls into the category of "folded fundus" as described by Boyden.[1]

The clinical significance of this finding is obvious. This paper is presented to call attention to a source of difficulty in the recognition of this congenital anomaly.

101 Medical Arts Building
Rochester 7, N. Y.

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* From the Bath Memorial Hospital, Bath, New York.

Fig. 1. Posteroanterior roentgenogram (*A*) and its tracing (*B*) show two overlapping ovoid shadows, each consistent with a gallbladder fundus. A second posteroanterior roentgenogram with 30° rotation to the left (*C*) and its tracing (*D*) again present essentially the same picture.

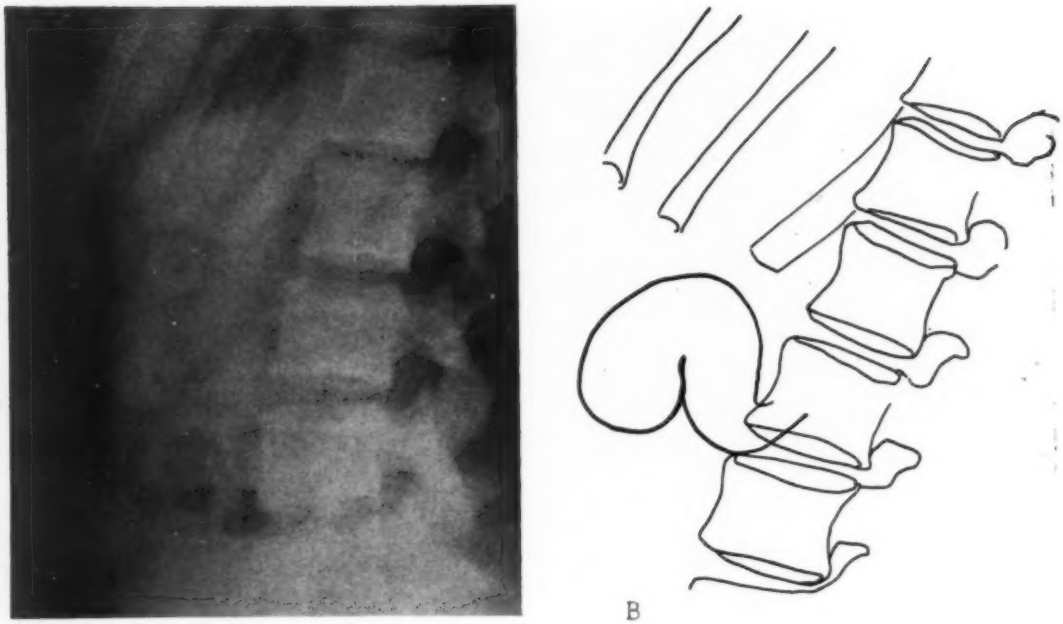

Fig. 2. Right lateral roentgenogram of the gallbladder area (*A*) and its tracing (*B*) clearly depict a "folded fundus" with superior angulation dividing the fundus into two major components.

THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

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Publisher: CHARLES C THOMAS, 301–327 East Lawrence Avenue, Springfield, Illinois.

Issued Monthly. Subscription $10.00 per year, $11.00 in Canada and $12.00 in foreign countries. Advertising rates submitted on application: Editorial office, 110 Professional Building, Detroit, Mich., Office of publication, 301–327 East Lawrence Avenue, Springfield, Ill. Information of interest to all readers will be found on page iv.

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Committee on Arrangements: To be appointed.

Thirtieth Annual Meeting: 1948, to be announced.

EDITORIALS

ANNUAL MEETING AMERICAN ROENTGEN RAY SOCIETY

THE Forty-Eighth Annual Meeting of the American Roentgen Ray Society will be held at Haddon Hall in Atlantic City from September 16 to 19, 1947. It has been nine years since the Society last met in Atlantic City and it will be nice to return to one of those delightful meeting places where the hotel in all its aspects lends itself so pleasantly to the comfort of the members and their guests and also its entertainment facilities are unexcelled.

President Elect J. Bennett Edwards and his Program Committee have arranged a program commensurate with the importance of the meeting and the meeting place. Elsewhere in this issue of the JOURNAL will be found the Preliminary Program for the September meeting. It may be readily seen, even from this preliminary report of the forthcoming meeting, that there are papers and symposia of great interest to radiologists.

The Caldwell Lecture, on Tuesday evening, which is always one of the outstanding features of the annual meetings, will be given this year by Dr. Merrill C. Sosman and he has chosen for his topic "Cushing's Disease—Pituitary Basophilism." Dr. Sosman is Professor of Radiology of the Harvard Medical School and is chief of the Department of Radiology of the Peter Bent Brigham Hospital. He is a Past President of the American Roentgen Ray Society and from his long association with Dr. Cushing he speaks with authority upon the subject which he has chosen to discuss.

Three interesting symposia have been arranged: One by Dr. Ralph S. Bromer on Pediatric Roentgenology, another by Dr. W. Walter Wasson on the Lesser Circulation and one by Dr. U. V. Portmann on Radiation Therapy. Distinguished members of the Society and guests will participate in these symposia.

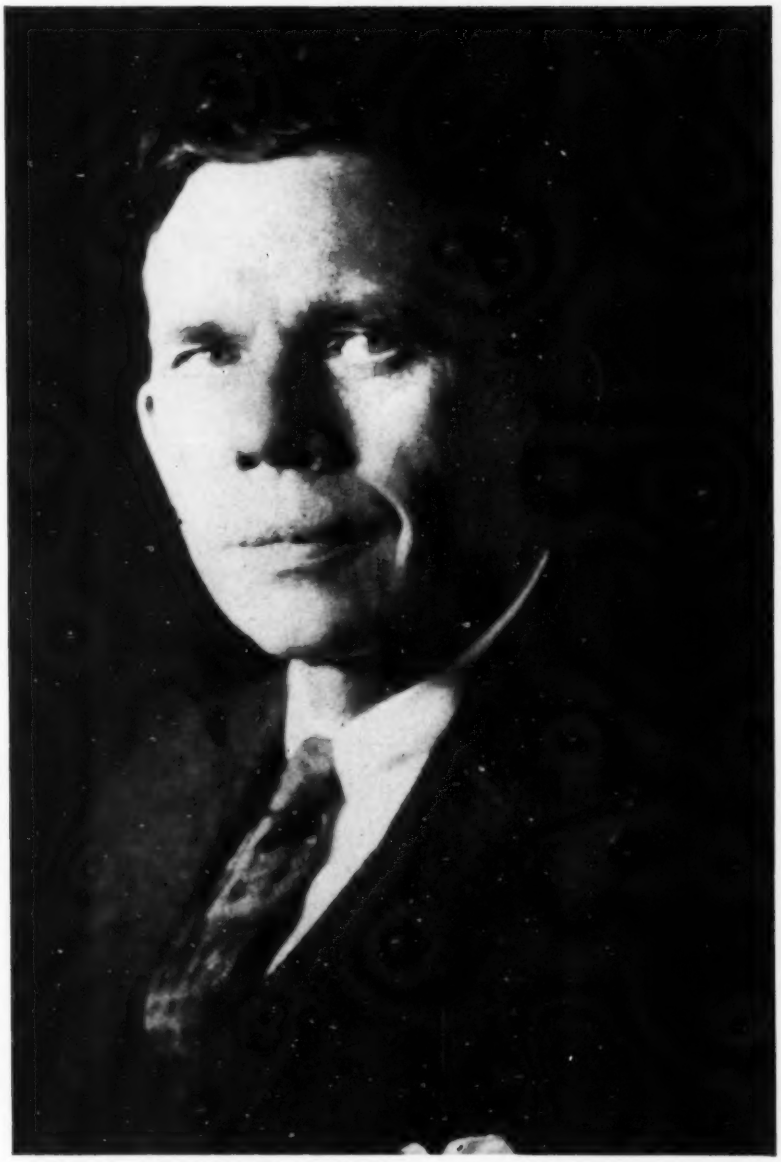
Under the directorship of Dr. B. R. Kirklin there will again be offered the Instruction Courses. These courses are always an important part of the program of the annual meetings and as arranged by Dr. Kirklin it is assured that the courses will be well worth attending. The courses will be given each day of the meeting from two to four-thirty in the afternoon. The program of the Instruction Courses will be published in the August issue of the JOURNAL.

Among the social features of the meeting will be the annual golf tournament on Monday in competition for the Manges Trophy. This is always an enjoyable affair. During the war years this feature, for obvious reasons, was discontinued but this year marks the resumption of the tournament and this will be welcomed by all the members of the Society.

On Thursday evening the Annual Banquet will be held and during the evening dancing and entertainment have been arranged for.

As is customary a Scientific Exhibit and a Technical Exhibit will be important parts of the meeting. Dr. R. A. Arens, Chairman of the Scientific Exhibit, has arranged an instructive group of exhibits. The Technical Exhibit this year promises to be a comprehensive one as the manufacturers have shown an unusual interest in the meeting and they are arranging attractive exhibits and no doubt will display many new and important designs in roentgenologic equipment.

Those who anticipate attending the meeting in Atlantic City should make their reservations immediately by writing to Haddon Hall.



CHARLES DARWIN ENFIELD
1887–1946

DR. CHARLES DARWIN ENFIELD died at his home in Louisville, Kentucky, November 14, 1946, after a protracted illness that necessitated his retirement from active practice early in January, 1946.

Dr. Enfield was born in Jefferson, Iowa, in 1887. He graduated from Rush Medical College in 1909 after which he served as an intern in Kansas City General Hospital, Kansas City, Missouri. He entered practice in Des Moines, Iowa, in October, 1910, remaining there until May, 1921, when he moved to Louisville, Kentucky, where he practiced, specializing in radiology, from

then until the time of his retirement. He was radiologist to St. Anthony's Hospital and the director of radiation therapy at the Norton Memorial Infirmary in Louisville, Kentucky.

Dr. Enfield was a man who had many friends and was held in high respect by his associates in and out of the medical profession. He was a keen student, had an inquiring mind and many interests. He was the author of one textbook and contributed many worthwhile articles to medical literature.

Dr. Enfield was a diplomate of the American Board of Radiology, a member of the American Roentgen Ray Society for many years; a Fellow of the American College of Physicians and of the American College of Radiology. He was a member of the American Medical Association, the Southern Medical Association, the Kentucky Medical Association and of a number of local medical societies. He was a member of the Medical Advisory Board of Selective Service during the recent war and was a member of the Association for the Study of Neoplastic Disease.

Dr. Enfield is survived by his wife and one son.

Joseph C. Bell

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer

MEETINGS OF THE ROENTGEN SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. H. Dabney Kerr, University Hospital, Iowa City, Iowa. Annual meeting: Haddon Hall, Atlantic City, N. J., Sept. 16–19, 1947.

AMERICAN RADIUM SOCIETY
Secretary, Dr. H. F. Hare, 605 Commonwealth Ave., Boston, Mass. Annual meeting: 1948, to be announced.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting: Hotel Statler, Boston, Mass., Nov. 30–Dec. 5, 1947.

AMERICAN COLLEGE OF RADIOLOGY
Secretary, Mac F. Cahal, 20 N. Wacker Drive, Chicago 6. Annual meeting: Haddon Hall, Atlantic City, N. J., June 8, 1947.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. U. V. Portmann, Cleveland Clinic, Cleveland, Ohio. Annual meeting: Atlantic City, N. J., June 9–13, 1947.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. C. S. Stickley, 515 Bell Bldg., Montgomery, Ala. Next meeting time and place of Alabama State Medical Association.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Fred Hames, 511 National Bldg., Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

BROOKLYN ROENTGEN RAY SOCIETY
Secretary, Dr. A. H. Levy, 1354 Carroll St., Brooklyn 13, N. Y. Meets monthly on fourth Tuesday, October to April.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph S. Gian-Francheschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months.

CENTRAL NEW YORK ROENTGEN RAY SOCIETY
Secretary, Dr. C. F. Potter, 820 S. Crouse Ave., Syracuse. Three meetings a year. January, May, November.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. T. J. Wachowski, 310 Ellis Ave., Wheaton, Ill. Meets second Thursday of each month October to April inclusive at the Palmer House.

CINCINNATI RADIOLOGICAL SOCIETY
Secretary, Dr. Eugene L. Saenger, 735 Doctors Bldg., Cincinnati 2, Ohio. Meets last Monday of each month, September to May, inclusive.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. George L. Sackett, 10515 Carnegie Ave. Cleveland 6, Ohio. Meetings at 6:30 P.M. on fourth Monday of each month from October to April.

DALLAS-FORT WORTH ROENTGEN STUDY CLUB
Secretary, Dr. X. R. Hyde, Medical Arts Bldg., Fort Worth, Texas. Meets in Dallas on odd months and in Fort Worth on even months, on third Monday, 7:30 P.M.

DENVER RADIOLOGICAL CLUB
Secretary, Dr. W. C. Huyler, 1619 Milwaukee, Denver 6, Colo. Meets third Friday of each month at Department of Radiology, Colorado School of Medicine.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. J. M. Dell, Jr., 333 W. Main St., S., Gainesville, Fla. Meetings in May and November.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. Robert Drane, DeRenne Apartments, Savannah, Ga. Meets in mid-winter and at annual meeting of Medical Association of Georgia in the spring.

RADIOLOGICAL SOCIETY OF KANSAS CITY
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

INDIANA ROENTGEN SOCIETY
Secretary, Dr. J. A. Campbell, Indiana University Hospitals, Indianapolis 7. Meets second Sunday in May.

IOWA X-RAY CLUB
Secretary, Dr. Arthur W. Erskine, 326 Higley Bldg., Cedar Rapids, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. Special meetings by announcement.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. W. C. Martin, 321 W. Broadway, Louisville. Meets annually in Louisville on first Saturday in Apr.

LONG ISLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

LOUISIANA RADIOLOGICAL SOCIETY
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society Meeting.

LOUISVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. E. L. Pirkey, Louisville General Hospital, Louisville 2, Ky. Meets monthly on second Friday at Louisville General Hospital.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS
Secretary, Dr. E. M. Shebesta, 1429 David Whitney Bldg., Detroit. Three meetings a year, Fall, Winter, Spring.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. C. A. H. Fortier, 231 W. Wisconsin Ave., Milwaukee, Wis. Meets monthly on second Monday at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Chauncey N. Borman, 802 Medical Arts Bldg., Minneapolis 2, Minn. Two meetings yearly, one at time of Minnesota State Medical Association the other in the fall.

* Secretaries of societies not here listed are requested to send the necessary information to the Editor.

Nebraska Radiological Society
Secretary, Dr. O. A. Neely, 924 Sharp Bldg., Lindoln, Neb. Meets third Wednesday of each month, at 6 P.M. at either Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. George Levene, Massachusetts Memorial Hospitals, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Ramsay Spillman, 115 East 61st St., New York City. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. J. E. Hemphill, 323 Professional Bldg., Charlotte 2, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. C. O. Heilman, 807 Broadway, Fargo. Meetings held by announcement.

Ohio Radiological Society
Secretary, Dr. Henry Snow, 1061 Reibold Bldg., Dayton, Ohio. Meets during annual meeting of Ohio State Medical Association.

Oklahoma State Radiological Society
Secretary, Dr. P. E. Russo, 230 Osler Bldg., Oklahoma City, Okla. Three regular meetings annually.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. J. M. Converse, 416 Pine St., Williamsport.

Philadelphia Roentgen Ray Society
Secretary, Dr. C. L. Stewart, Jefferson Hospital. Meets first Thursday of each month, October to May, at 8:00 P.M., in Thomson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. L. M. J. Freedman, 115 South Highland Ave. Meets 6:30 P.M. at Webster Hall Hotel on second Wednesday each month, October to May inclusive.

Portland Roentgen Club
Secretary, Dr. Selma Hyman, University of Oregon Medical School, Portland, Oregon. Meets monthly 2d Wednesday, 8:00 P.M., Library of University of Oregon Medical School.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Harry A. Miller, 2452 Eutaw Place, Baltimore. Meets third Tuesday each month, September to May.

Radiological Section, Connecticut Medical Society
Secretary, Dr. Robert M. Lowman, Grace-New Haven Community Hospital, New Haven 11, Conn. Meets bimonthly on second Thursday, at place selected by Secretary.

Radiological Section, Los Angeles Co. Med. Assn.
Secretary, Dr. Moris Horwitz, 2009 Wilshire Blvd., Los Angeles 5, Calif. Meets on second Wednesday of each month at the County Society Building.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of New Jersey
Secretary, Dr. Raphael Pomeranz, 31 Lincoln Park, Newark, N. J. Meets annually at time and place of State Medical Society. Mid-year meetings at place chosen by president.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Murray P. George, Strong Memorial Hospital. Meets monthly on third Monday from October to May, inclusive, 8 P.M. at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary Dr. A. M. Popma, 220 N. First St., Boise, Idaho. Mid-Summer Conference, Shirley Savoy Hotel, Denver, Colo., Aug. 7, 8, 9, 1947.

St. Louis Society of Radiologists
Secretary, Dr. Edwin C. Ernst, Beaumont Medical Building, St. Louis, Mo. Meets fourth Wednesday of each month, except June, July, August, and September.

San Diego Roentgen Society
Secretary, Dr. R. F. Niehaus, 1831 Fourth Ave., San Diego, Calif. Meets monthly, first Wednesday at dinner.

Section on Radiology, California Medical Association
Secretary, Dr. D. R. MacColl, 2007 Wilshire Blvd., Los Angeles 5, Calif.

Section On Radiology, Illinois State Medical Society
Secretary, Dr. H. W. Ackemann, 321 W. State St., Rockford, Ill.

Shreveport Radiological Club
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

South Carolina X-Ray Society
Secretary, Dr. T. A. Pitts, Baptist Hospital, Columbia, S. C. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. J. M. Frère, 707 Walnut St., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth 4, Texas.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May inclusive. Room 203, Service Memorial Institute, 426 N. Charter St., Madison.

Utah Radiological Conference
Secretary, Dr. Henry H. Lerner, School of Medicine, University of Utah, Salt Lake City 1. Meets 1st and 3rd Thursdays monthly from 7:30 to 10 P.M., Salt Lake County General Hospital, September to June.

Utah State Radiological Society
Secretary, Dr. M. Lowry Allen, Judge Bldg., Salt Lake City 1, Utah. Meets third Wednesday in September, November, January, March and May.

Virginia Radiological Society
Secretary, Dr. E. L. Flanagan, 116 E. Franklin St. Richmond, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Thomas Carlile, 1115 Terry St., Seattle. Meets fourth Monday each month, October through May, College Club, Seattle.

X-Ray Study Club of San Francisco
Secretary, Dr. Ivan J. Miller, 2000 Van Ness Ave. Meets monthly on third Thursday at 7:45 P.M., first six months of year at Lane Hall, Stanford University

Hospital, and second six months at Toland Hall, University of California Hospital.

Cuba

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Mexico

Sociedad Mexicana de Radiologia y Fisioterapia
General Secretary, Dr. D. P. Cossio, Marsella No. 11, Mexico, D. F. Meets first Monday of each month.

British Empire

British Institute of Radiology Incorporated with the Roentgen Society
Medical Members' meeting held monthly on third Friday at 2:30 P.M. and Ordinary Meeting at same time on following Saturday, October to May, 32 Welbeck St., London, W.1.

Faculty of Radiologists
Secretary, Dr. M. H. Jupe, 23 Welbeck St., London, W.1 England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary, Dr. E. M. Crawford, 2100 Marlowe Ave., Montreal 28, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Francaise d'Electrologie et de Radiologie Médicales
Secretary, Dr. Origéne Dufresne, 4120 Ontario St., East, Montreal, P. Q.

Radiological Section of the Victorian Branch of the British Medical Association
Secretary, Dr. Keith Hallam, St. George's Hospital. K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to November inclusive.

Section of Radiology and Medical Electricity, Australasian Medical Congress
Secretary, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section, New Zealand British Medical Association
Secretary, Dr. Colin Anderson, Invercargill, New Zealand. Meets annually.

South America

Sociedad Argentina de Radiologia
Secretary, Dr. Guido Gotta, Buenos Aires, Argentina. Meetings are held monthly.

Sociedad Peruana de Radiologia
Secretary, Dr. Julio Bedoya Paredes, Apartado, 2306 Lima, Peru. Meetings held monthly except during January, February and March, at the Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

Continental Europe

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 111 Avenue des Alliés, Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Ceskoslovenská společnost pro röntgenologii a radiologii v Praze
Secretary, MUDr. Roman Blána, Praha XII, Korunní 160, Czechoslovakia.

Polish Society of Radiology
First post-war inaugural meeting will be held in Warsaw, May 22 and 23, 1947.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, Nowogrodzka 59, Warsaw, Poland. Meets monthly.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad: USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock, State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly, first Monday, 8 P.M.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
Secretary for French language, Dr. Babaiantz, Geneva.
Secretary for German language, Dr. Max Hopf, Effingerstrasse 49, Bern. Meets annually in different cities.

PRELIMINARY PROGRAM

FORTY-EIGHTH ANNUAL MEETING OF THE AMERICAN ROENTGEN RAY SOCIETY

The Forty-eighth Annual Meeting of the American Roentgen Ray Society will be held at Haddon Hall, Atlantic City, New Jersey, on September 16, 17, 18 and 19, 1947.

The Executive Council will meet at noon on Sunday, September 14.

The annual Golf Tournament for the Willis F. Manges Trophy will be held on Monday, September 15, at the Seaview Country Club, Absecon, New Jersey.

The Caldwell Lecture will be given on Tuesday evening, September 16 at 8:30 and the Annual Banquet will be held on Thursday evening, September 18.

The Scientific Sessions will begin each morning at 8:30 A.M. and the Instruction Courses will begin each afternoon at 2:00 P.M. A detailed schedule of the Instruction Courses will be published in the August issue of the JOURNAL.

The scientific program has been tentatively arranged as follows:

Tuesday, September 16, 1946

8:30 A.M. Call to order. Raymond C. Beeler, M.D., President

Address of Welcome. (To be announced.)

Installation of the President-Elect, J. Bennett Edwards, M.D.

Inaugural Address. (To be given by Ross Golden, M.D.)

9:40 A.M. Symposium on Pediatric Roentgenology. Arranged by Ralph S. Bromer, M.D.

1. Infantile Torulosis. Edward B. D. Neuhauser, M.D. (by invitation), Boston, Mass.
2. Common Roentgenologic Findings in Pyuria. Meredith F. Campbell, M.D. (by invitation), New York, N. Y.
3. Roentgen Diagnostic Criteria in Congenital Heart Disease. John W. Pierson, M.D., and John J. Douglas, M.D. (by invitation), Baltimore, Md.
4. The Skeletal Lesions in Leukemia; Roentgenographic Observations in Infants and Children. Frederic N. Silverman, M.D. (by invitation), New York, N. Y.
5. The Significance of Triangular Hilar Shadows in Roentgenograms of Infants and Children. Rolfe M. Harvey, M.D. (by invitation), and Ralph S. Bromer, M.D., Bryn Mawr, Pa.

Tuesday, Wednesday, Thursday and Friday

2:00-4:30 P.M. Instruction Courses

Tuesday Evening, September 16, 1947

Eight-Thirty O'Clock

The Caldwell Lecture

Merrill C. Sosman, M.D.

Professor of Radiology, Harvard Medical School

"Cushing's Disease—Pituitary Basophilism"

Wednesday, September 17, 1947

8:30 A.M. Symposium on The Lesser Circulation. Arranged by W. Walter Wasson, M.D.

6. The Anatomy and Physiology of the Lesser Circulation. L. R. Sante, M.D., St. Louis, Mo.
7. The Roentgen Appearance of the Chest in Certain Diseases Affecting the Peripheral Vessels of the Lungs. Robert P. Barden, M.D., Philadelphia, Pa.
8. The Heart and the Congenital Anomalies and Their Relation to the Lesser Circulation. Lewis Dexter, M.D. (by invitation), Boston, Mass.
9. The Lesser Circulation as Observed by the Anesthetist. Robert D. Dripps, M.D. (by invitation), Philadelphia, Pa.
10. The Evaluation of the Lesser Circulation as Portrayed by the Roentgen Film. W. Walter Wasson, M.D., Denver, Colo.
11. Clinical Observations of the Lesser Circulation. Leo G. Rigler, M.D., Minneapolis, Minn.

Thursday, September 18, 1947

8:30 A.M.

12. Monostotic Fibrous Dyplasia. George M. Wyatt, M.D., Washington, D. C.,

and W. S. Randall, Jr., M.D. (by invitation), New Orleans, La.

13. The Gastric Cancer Problem: Methods of Attack and Their Present Status. Frederic E. Templeton, M.D., Seattle, Wash.
14. Small Intestinal Motility in Dysentery. George P. Keefer, M.D. (by invitation).
15. Pyloric Obstruction, More Accurately Demonstrated by Food-Barium Mixture Vincent W. Archer, M.D., George Cooper, Jr., M.D., and Norman Adair, M.D. (by invitation), Charlottesville, Va.
16. Incidence of Carcinoma of the Stomach in a Large Series of Roentgen Examinations. B. R. Kirklin, M.D., and J. R. Hodgson, M.D. (by invitation), Rochester, Minn.
17. The Effects of Intrathoracic Pressure Changes on the Systolic and Diastolic Size of the Heart. Marcy L. Sussman, M.D., New York, N. Y.

Thursday Evening, September 18, 1947

Seven-Thirty O'Clock
Annual Banquet

Friday, September 19, 1947

8:30 A.M. Symposium on Radiation Therapy. Arranged by U. V. Portmann, M.D.

18. Roentgen Therapy of Pituitary Adenomas. H. Dabney Kerr, M.D., Iowa City, Iowa.
19. Carcinoma of the Bladder. Albert E. Bothe, M.D. (by invitation), Philadelphia, Pa.
20. Roentgen Therapy of Carcinoma of the Larynx and Pharynx. A. U. Desjardins, M.D., and F. A. Figi, M.D. (by invitation), Rochester, Minn.
21. Chondronecrosis of the Larynx following Roentgen Therapy. William A. Goodrich, M.D. (by invitation), and Maurice Lenz, M.D., New York, N. Y.
22. Post-irradiation Ulcerations of the Uterine Cervix. Harold W. Jacox, M.D., New York, N. Y.
23. Irradiation Injuries to the Urinary and Intestinal Tract Following the Use of Low Intensity Long Element Needles in the Treatment of Carcinoma of the Cervix Uteri. George W. Waterman, M.D. (by invitation), and Ellsworth Tracy, M.D. (by invitation), Providence, R. I.
24. Colloidal Lead Associated with Deep Roentgen Therapy in Bone Metastasis. Lawrence Reynolds, M.D., T. Leucutia, M.D., K. E. Corrigan, Ph.D., and James C. Cook, M.D. (by invitation), Detroit, Mich.
25. Dosage Determination with Radioactive Isotopes. L. D. Marinelli, Ph.D. (by invitation), Edith H. Quimby, Sc.D., and G. J. Hine, Ph.D. (by invitation), New York, N. Y.

ALABAMA RADIOLOGICAL SOCIETY

At a recent meeting of the Alabama Radiological Society the following officers were elected for the coming year: *President*, Dr. John D. Peake; *Vice-President*, Dr. L. E. Sorrell; *Secretary-Treasurer*, Dr. C. S. Stickley. Dr. Karl Kesmodel was nominated as candiate for Councilor to the American College of Radiology.

RADIOLOGICAL SOCIETY OF NEW JERSEY

At a recent meeting of the Radiological Society of New Jersey the following officers were elected for the coming year: *President*, Dr. H. R. Brindle, Asbury Park, N. J.; *Vice-President*, Dr. William H. Seward, Orange, N. J.; *Secretary*, Dr. Raphael Pomeranz, Newark, N. J.; *Treasurer*, Dr. C. A. Plume, Succasunna, N. J.

TENNESSEE RADIOLOGICAL SOCIETY

At the recent annual meeting of the Tennessee Radiological Society the following officers were elected for the coming year: *President*, Dr. J. Cash King, Memphis, Tenn.; *Vice-President*, Dr. Franklin B. Bogart, Chattanooga, Tenn.; *Secretary-Treasurer*, Dr. J. Marsh Frère, Chattanooga, Tenn. Dr. U. V. Portmann, Cleveland Clinic, Cleveland, Ohio, was guest speaker on the program of the Tennessee State Medical Association. He gave a most interesting and instructive paper on "The Role of Surgery and Radiation Therapy for Cancer of the Breast." He spoke to the Tennessee Radiological Society on "Roentgen Therapy for some Superficial Lesions."

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ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

ROENTGEN DIAGNOSIS

HEAD

McCLURE, GEORGE. Odontoma of the nasopharynx. *Arch. Otolaryng.*, July, 1946, *44*, 51–60.

As long ago as 479 B.C. Herodotus described a skull found in the battle of Plataea, in which each jaw contained teeth that were fused in a mass.

The calcified tumor is usually seen early in life, in either sex, as a slow growing, painless swelling. It is usually associated with unerupted teeth and occurs in the molar region of either the mandible or the maxilla. The tumor is an encapsulated calcified structure containing enamel, dentin and cementum. The complex composite odontoma is characterized by a conglomerate mass of calcified tooth structure composed of enamel, dentin and cementum. The compound composite odontoma, on the other hand, is an encapsulated tumor containing numerous teeth, portions of teeth or denticles.

Any tumor of the nasopharynx is uncommon, but a true odontoma of that area is rare indeed. In fact an odontoma of the nasopharynx has never before been described. The summary and comment on the case reported are as follows:

1. The character of the growth with the deciduous tooth puts it in the classification of osteofibroma of dentigerous origin.

2. The location is unusual, rare for this type of tumor.

3. The origin of the growth could not be determined, but apparently the tumor sprang from the posterior ramus of the mandible. A tumor of this type when situated within the mandible or the maxilla appears to be completely separated from the surrounding bone by its capsule; therefore, one may assume that this tumor had no attachment.

4. The audiogram reveals a typical conductive hearing loss in the left ear due either to complete obstruction or to absence of the eustachian tube.

5. The recurrence of the tumor was definitely due to a small portion of the capsule in the extreme lateral part remaining. This contained tooth remnants in the bony structure with the power of regrowth. This regrowth is typical of odontoma, with the second tooth presenting itself to the surface—in this case, the nasopharynx.

6. The recurrence of growth and the formation of a second deciduous tooth definitely put the tumor in the classification of compound composite odontoma.—*Mary Frances Vastine.*

NECK AND CHEST

Clagett, O. Theron; Payne, John H., and Moersch, Herman J. Acquired esophagotracheobronchial fistula. *Surg., Gynec. & Obst.*, Jan., 1946, *82*, 87–90.

Since the trachea and the upper part of the esophagus lie in close apposition, it is easy to understand how a pathologic process of one organ may spread and involve the other organ secondarily.

Causes.

1. Malignant disease of the esophagus
2. Infectious disease of the esophagus, trachea or pleura
   - A. Tuberculosis
   - B. Syphilis
   - C. Fungus infections
   - D. Suppurative esophagitis
   - E. Non-tuberculous empyema
3. Traumatic injuries of the esophagus
4. Esophageal diverticula
5. Esophagomalacia

Carcinoma of the esophagus is the most frequent cause of fistula formation. Ewald stated that 50 per cent of carcinomas of the middle third of the esophagus are associated with fistula.

Symptoms. As a rule, congenital tracheoesophageal fistulas manifest their presence at once by a definite group of symptoms; acquired fistulas may be present for varying periods before they produce symptoms. There is usually a history of varying degrees of dysphagia gradually increasing in severity. Then suddenly cough develops as well as dyspnea when the patient eats and he raises purulent sputum and occasionally blood.

Treatment. When fistula arises from malignant disease, there is no treatment available. Some of the other types of fistula are amenable to various forms of therapy. Clerf, Cooley, and O'Keefe have reported 2 cases in which esophagotracheal fistula was successfully treated by the application of crystals of sodium hydroxide.

Imperatori has reported a case in which a high fistula was treated by excising the fistulous tract and closing the esophagus and trachea separately with interrupted sutures.

When these fistulas arise from empyemas, Cohen and Sindell advocate adequate drainage of the pleura and prolonged esophageal rest by the use of nasal tube feedings or gastrostomy feedings. This regimen is followed until the esophageal fistula has had adequate time to heal.—*Mary Frances Vastine.*

Lahey, Frank H., and Ficarra, Bernard J. The lateral aberrant thyroid. *Surg., Gynec. & Obst.*, June, 1946, *82*, 705–511.

Forty-seven tumors of lateral aberrant thyroid origin were encountered at the Lahey Clinic up to July 1, 1945. During this same period 25,000 patients were treated for various types of goiter. Thus, one tumor of this type is seen in approximately every 500 goiter patients.

As a result of their investigations along this line, the authors arrive at the following conclusions:

1. Tumors of lateral aberrant thyroid origin arise from the ultimobranchial body as a result of departure from normal embryologic development.

2. These tumors may occur in patients of any age, but they are seen more often under forty years of age—in women.

3. The diagnosis can usually be made clinically and this must be confirmed by biopsy.

4. The differential diagnosis must include tuberculosis, lymphosarcoma, Hodgkin's disease, inflammatory glands, metastatic carcinoma, the simple neck tumors, branchial cysts, carotid body tumors and neurofibromas.

5. The characteristic pathologic picture is a papillary cystadenomatous structure showing little, if any, differentiation into adult thyroid structure. All these tumors must be considered as actually or potentially malignant.

6. Radical neck dissection followed by deep radiation therapy is the most satisfactory course of treatment. This lesion is of low malignancy and is radiosensitive.

7. The operative mortality in 47 cases was zero.

8. Follow-up studies of 30 patients prior to 1939 cover a period of five to fifteen years. Twenty-one of these patients showed no recurrence; 4 had recurrence, were reoperated upon, and have remained well. Four died of other causes. One patient died of recurrent malignant disease of lateral aberrant thyroid origin.

9. Follow-up study of the authors' most recent 17 cases encompasses the past six years. One patient had a recurrence, was reoperated upon twice and has remained well.

10. Whenever a biopsy specimen is taken of a tumor from the lateral region of the neck, and

the report is papilliferous cystadenoma or papillary adenocarcinoma, in all probability it is a lateral aberrant thyroid.—*Mary Frances Vastine.*

Lell, William A. Bronchoscopy as an aid in the diagnosis and treatment of allergic pulmonary disease. *Arch. Otolaryng.*, Jan., 1946, *43*, 49–58.

Bronchoscopic Diagnosis and Treatment of Conditions Simulating Asthma. A foreign body may produce symptoms of asthma. This is true particularly in children, with whom a history of foreign body may be entirely unsuspected. *The routine in the roentgen examination of these patients includes:* (1) anteroposterior and lateral projections of the neck; (2) inspiration and expiration roentgenograms of the chest in both the anteroposterior and lateral view; (3) a careful fluoroscopic study with an opaque mixture and (4) roentgenograms of the swallowing function.

In a review of the record of 176 children admitted for bronchoscopic examination because of symptoms simulating asthma, which had not readily responded to the orthodox treatment, the following diagnoses were made:

Retropharyngeal abscess	1
Foreign body in larynx	5
Organic changes in the larynx	8
Tracheal compression	14
Bronchial foreign body	13
Esophageal foreign body	5
True asthma, little secretion	47
True asthma, thick secretion	83

Characteristic Bronchoscopic Findings in Allergic Pulmonary Disease. The author's observations in a large number of cases of asthma have not confirmed the classic description of the blanched appearance of the mucous membrane and the presence of thick, sticky secretion purported to be associated with asthma.

The same person may present entirely different findings at different times depending on whether the examination is made while the patient is suffering from an acute attack or at a short or a long interval after an attack. This is particularly true of children. If the examination is made at a long interval after an attack, a practically normal appearance is presented, the mucous membrane being smooth and velvety with absence of inflammatory reaction or expiratory collapse of the posterior tracheal wall.

On the other hand, in all patients examined during an attack, whether children or adults, the changes are fairly constant and uniform: The mucous membrane is hemorrhagic, red and redundant, greatly reducing the caliber of the lumen of the trachea and both main bronchi. Secretions are always present and so tenacious that they are difficult to aspirate. The classic phenomenon of collapse of the posterior tracheal wall is frequently present in children and almost always present in adults during status asthmaticus.

Pathologic Changes in Status Asthmaticus. (1) Engorgement of the epithelial cells, thickening of the basement membrane, hypertrophy of the muscle bundles and increase in size of the mucous glands. (2) Marked prominence of the lymphoid connective tissue and eosinophilic cells in the subepithelial and extramuscular layers.

Bronchoscopy in the Treatment of Asthma. An uncontaminated specimen of secretion from the bronchial tree can be obtained. By determining the type of organism present, the proper drug can be administered. (These drugs may be administered bronchoscopically with unusually effective results.)

Autogenous vaccine is a valuable adjunct to therapy in these patients. In the majority of cases the vaccine serves to immunize the patient against the organisms which he harbors and renders him less susceptible to recurrent infections of the respiratory tract. The author's observations have shown that in at least 65 per cent of the patients, attacks of status asthmaticus were preceded by acute infections of the respiratory tract. The roentgen examination of the chest during this phase revealed marked accentuation of the hilar markings and, in many cases, even of the mediastinal shadow.

Of great importance during the bronchoscopic aspiration is the hypodermic injection of a solution of epinephrine hydrochloride made just before the bronchoscopy. The secretion is more readily aspirated and the patient experiences more promptly, effective and permanent relief following the injection of epinephine (or theophylline ethylenediamine).

Bronchoscopy in the Treatment of Status Asthmaticus. A series of 269 bronchoscopic examinations and aspirations have been performed on 102 patients. In all cases, during the bronchoscopic examination oxygen was administered through an attachment on the bronchoscope, thereby relieving the dyspnea.

Of utmost importance in the treatment of patients subject to asthmatic attacks, if the

greatest relief is to be obtained, is that they be given the treatment as soon as possible during an attack, whether it is in the middle of the night or during the day.—*Mary Frances Vastine.*

Hartzell, Homer C., and Mininger, Edward P. Bronchopneumonia following ether anesthesia in obstetrics. *Surg., Gynec. & Obst.*, April, 1946, *82*, 427–433.

A series of cases of bronchopneumonia has been observed in patients on the obstetrical service at Cleveland City Hospital. These bronchopneumonias, observed within a few days following delivery, were variable in extent, transient in nature, and were not associated with clinical evidence of serious illness. They were discovered in almost all cases by means of a roentgenogram of the chest made to investigate the significance of slight fever or rales in the chest developing after delivery. The anesthesia in these cases consisted of ether administered usually by the open method and preceded by varying quantities of barbiturate and other premedication. The mechanism by which the pneumonias were produced was probably the aspiration of mucus or vomitus during or following anesthesia. Other factors which may be considered are suppression of cough reflex and retention of secretions due to the irritation of ether.

Evaluation of Study. The frequent involvement of the right side as compared with the left may be explained by the more vertical course and larger caliber of the right main bronchus as compared with its fellow on the left. Similar predominance of right-sided involvement has been observed in aspiration of foreign bodies and in lung abscess.

The lobar distribution of the aspiration pneumonias emphasizes merely that in bed patients such changes are not confined to the bases, but may occur anywhere in the lungs.

There was no correlation between the extent of the pneumonia and the quantity of sedative medication administered.

No difference was apparent in the clinical course of those patients treated with chemotherapy and those left untreated.

Vomiting is known to have occurred during anesthesia or labor in 9 of 20 cases in this series. It is possible that in additional cases vomiting took place prior to anesthesia or following its completion, but was not recorded. It is also possible that the aspiration of mucus, in the absence of frank vomiting, may result in aspiration pneumonia.

Roentgenologic Findings. In localization, involvement of the right side was more frequent than the left. Involvement of the upper lung was more frequent than the lower. The most frequent single site of localization was the right upper lobe area.

The less extensive cases have presented the picture of "soft" fluffy localized shadows of increased density which, when situated in the upper lung fields, closely simulate the early infiltrations of adult tuberculosis.

The more extensive bilateral cases have shown symmetric extensive coalescent densities, with tendency to central localization, simulating the picture of pulmonary edema.

Usually an associated generalized increase in prominence of the vessel markings has been found, suggestive of pulmonary hyperemia. None of the patients have shown mediastinal displacement or other evidence of massive atelectasis.

Clearing of the infiltration was rapid in most cases and complete in all. Fifteen of 18 cases in which serial films were available showed complete clearing in one week or less.

On strictly objective criteria, a roentgenologic diagnosis of aspiration pneumonia is not possible, but its recognition is usually easy if the roentgenologist has the clinical findings available to him, and if he is familiar with the condition.

Summary and Conclusions. A series of 20 cases of bronchopneumonia developing following obstetrical delivery in which ether anesthesia was used have been observed.

The chief cause was the aspiration of gastric contents as a result of vomiting. The following were probably contributory: (1) preanesthetic medication favoring suppression of the cough reflex, (2) prolonged gastric evacuation in labor, (3) fluidity of gastric contents, favoring their dissemination in the bronchial tree.

The bronchopneumonias varied in extent from small isolated patches to extensive bilateral infiltrations.

Clinically they did not prove a cause of serious illness and no fatalities resulted. Chemotherapy by sulfonamide drugs was apparently not effective.

Roentgenologically, the problem was one of differentiation from pulmonary tuberculosis, sarcoidosis, other pneumonias, pulmonary edema, and atelectasis.—*Mary Frances Vastine.*

AUERBACH, OSCAR. Laryngeal tuberculosis. *Arch. Otolaryng.*, Aug., 1946, *44*, 191–201.

In the course of autopsies by the author and his colleagues, the larynx was routinely examined for gross and microscopic pathologic changes. An opportunity was thus afforded to study the mode of development and the progression of laryngeal tuberculosis as well as its relationship to tuberculosis in other parts of the body.

Conclusions:

1. Laryngeal tuberculosis was present in 37.5 per cent of the cases of tuberculosis (304) which came to autopsy.

2. In all but two instances it developed as a direct infection from positive sputum in chronic pulmonary tuberculosis.

3. The age, sex and race distributions in this series parallel those in chronic pulmonary tuberculosis, i.e.,

Age: 20–39 years

Sex: 208 males to 96 females.

Race: 185 Caucasians, 116 Negroes and 3 Asiatics.

4. Tuberculous foci, with and without central zones of caseation, form in the walls of the larynx as a result of tubercle bacilli which enter through the ducts of the mucous glands. Ulceration develops either through pressure atrophy of the mucous membrane by the tuberculous foci or by caseous necrosis of the overlying epithelium as the tuberculous areas enlarge. The further progression of the ulcerative process is similar to that in other parts of the body. Ulcers were found most frequently on the true vocal cords (47.1 per cent).

5. Healing may occur in any stage of anatomic development, usually in cases in which the underlying chronic pulmonary tuberculosis undergoes anatomic healing. In some instances healing and progression keep pace in the same larynx, resulting in a pronounced thickening of the wall, nodular protrusions into the lumen and narrowing of the canal.—*Mary Frances Vastine.*